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UNITED STATES PATENT APPLICATION

FOR

TREATMENT AND PREVENTION OF OTIC DISORDERS WITH COX-2 INHIBITORS ALONE OR IN COMBINATION WITH OTIC AGENTS

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TREATMENT AND PREVENTION OF OTIC DISORDERS WITH COX-2 INHIBITORS ALONE OR IN COMBINATION WITH OTIC AGENTS

CROSS REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

[0001] This application is related to and claims the priority benefit of U.S. Provisional Patent Application Serial No. 60/456,286, filed March 20, 2003, which is incorporated by reference herein in its entirety.

BACKGROUND OF THE INVENTION

(1) Field of the Invention:

[0002] The present invention relates to the prevention and treatment of otic diseases and disorders and otic disorder-related complications, and more particularly to the prevention and treatment of otic diseases and disorders and otic disorder-related complications with a cyclooxygenase-2 inhibitor alone or in combination with otic agents.

(2) Description of the Related Art:

[0003] Otic disorders rank second only to the common cold as the most frequent illness among children in the United States. Most otic disorders are the result of a painful inflammatory response to infections, allergic reactions, or trauma to the ear. An otic infection may be of bacterial, fungal or viral origin and determination of the precise etiology is not practical since the causative organism is often difficult to isolate and culture.

[0004] The most common otic disorder, otitis media, is a leading cause of hearing loss in the United States and represents a significant disability interfering with childhood learning processes. *See* Estrada, B., *Infect. Med. 14(3)*:239-44 (1997). Otitis media accounts for over 35 percent of all childhood visits to pediatricians each year and represents more than $3.5 billion in U.S. health care costs annually.

[0005] Otitis media is a painful disorder of the middle ear that is usually accompanied by fever, swelling and inflammation of the eardrum and considerable pain. Otic disorders frequently strike younger children

because, anatomically, the eustachian tubes in infants are shorter, wider, and lie more horizontally than in older children and adults. Such an anatomical difference facilitates the spread of pathogens from the nasopharnyx to the middle ear. This can result in infection, which can evoke a painful inflammatory response in the mucosal tissue of the middle ear.

[0006] Typically, otic disorders such as otitis media are treated with a course of antibiotic therapy. *See The Merck Manual of Diagnosis & Therapy, Beers & Brakow, 17th edition,* Published by Merck Research Labs, *Sec. 7, Chapter 84, ENT Disorders, Acute Otitis Media* (1999). Antibiotic therapy is generally indicated to relieve symptoms, hasten resolution of the infection, and reduce the chance of complications and of residual damage to the hearing mechanism in the middle ear. *Id.*

[0007] Unfortunately, antibiotic therapy is mainly effective for treating the underlying infection and does not address the associated pain and inflammation. Subjects suffering from an otic disorder would, historically, have to take multiple separate medications to treat both the underlying disorder and the associated pain and inflammation. Therefore, it would be very advantageous to have a combination therapy that would alleviate the infectious process as well as the inflammation that accompanies it. This would mean greater ease for the doctor and for the subject and would improve the degree to which the treatment is followed.

[0008] Moreover, due to the widespread use of antibiotics, organisms that are antibiotic-resistant are becoming increasingly common. *See* Klein, J., *Am. J. Manag. Care 8(14 Suppl)*:S345-52 (2002). Thus, new therapies that eliminate or reduce the required dosage of antibiotics would also be useful.

[0009] Historically, physicians have treated inflammation-related disorders with a regimen of nonsteroidal anti-inflammatory drugs (NSAIDs), such as, for example, aspirin and ibuprofen. Undesirably, however, some NSAIDs are known to cause gastrointestinal (GI) bleeding

or ulcers in subjects undergoing consistent long-term regimens of NSAID therapy.

[00010] A reduction of unwanted side effects of common NSAIDs was made possible by the discovery that two cyclooxygenases are involved in the transformation of arachidonic acid as the first step in the prostaglandin synthesis pathway. These enzymes exist in two forms and have been termed cyclooxygenase-1 (Cox-1) and cyclooxygenase-2 (Cox-2). *See* Needleman, P., *et al., J. Rheumatol. 24, Suppl.49*:6-8 (1997) and Fu, J., *et al., J. Biol. Chem. 265(28)*:16737-40 (1990).

[00011] Cox-1 is a constitutive enzyme responsible for the biosynthesis of prostaglandins in the gastric mucosa and in the kidney. Cox-2 is an enzyme that is produced by an inducible gene that is responsible for the biosynthesis of prostaglandins in inflammatory cells. Inflammation causes the induction of Cox-2, leading to the release of prostanoids (prostaglandin E2), which sensitize peripheral nociceptor terminals and produce localized pain hypersensitivity, inflammation and oedema. *See e.g.* Samad, T. A. *et al., Nature 410*(6827):471-5 (2001). Many common NSAIDs are now known to be inhibitors of both Cox-1 and Cox-2. Accordingly, when administered in sufficiently high levels, these NSAIDs not only alleviate the inflammatory consequences of Cox-2 activity, but also inhibit the beneficial gastric maintenance activities of Cox-1.

[00012] Research into the area of arachidonic acid metabolism has resulted in the discovery of compounds that inhibit the Cox-2 enzyme to a greater extent than the activity of Cox-1. The Cox-2-selective inhibitors are believed to offer advantages that include the capacity to prevent or reduce inflammation while avoiding harmful side effects associated with the inhibition of Cox-1. Thus, Cox-2 selective inhibitors have shown great promise for use in therapies -- especially in therapies that require long-term administration, such as for pain and inflammation control.

[00013] While the effects of Cox-2 inhibitors on inflammation and inflammation-related disorders have been relatively widely recognized, the

effects of Cox-2 inhibitors on otic diseases and disorders have not been as widely reported. In fact, certain Cox-2 inhibitors, for example, aspirin, have been contraindicated for otic disorders because of aspirin's implication as a causative agent in at least one otic disorder. *See* U.S. Patent No. 6,265,379 to Donovan.

[00014] Despite the recent advances that have been made in understanding the causes of otic disorders, they remain largely unpreventable and are difficult to effectively treat. It would be useful, therefore, to provide efficacious methods and compositions for the prevention and treatment of otic disorders and otic disorder-related complications.

SUMMARY OF THE INVENTION

[00015] Briefly, therefore, the present invention is directed to a novel method of preventing or treating otic disorders and otic-disorder-related complications in a subject comprising administering to the subject a Cox-2 inhibitor.

[00016] The present invention is also directed to a novel method of preventing or treating otic disorders and otic-disorder-related complications in a subject that is in need of such prevention and treatment comprising administering to the subject a Cox-2 inhibitor.

[00017] The present invention is also directed to a novel method of preventing and treating otic disorders and otic disorder-related complications in a subject comprising administering to the subject a Cox-2 inhibitor and one or more otic agents.

[00018] The present invention is also directed to a novel method of preventing and treating otic disorders and otic disorder-related complications in a subject that is in need of such prevention and treatment comprising administering to the subject a Cox-2 inhibitor and one or more otic agents.

[00019] The present invention is also directed to a novel therapeutic composition comprising a Cox-2 inhibitor and an otic agent.

[00020] The present invention is also directed to a novel pharmaceutical composition comprising a Cox-2 inhibitor, an otic agent, and a pharmaceutically acceptable carrier.

[00021] The present invention is also directed to a novel kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising an otic agent.

[00022] Among the several advantages found to be achieved by the present invention, therefore, may be noted the provision of improved treatment methods and compositions for otic disorders, the provision of such improved methods and compositions comprising Cox-2 inhibitors alone and in combination with one or more otic agents that are useful for treating and preventing otic disorders and otic disorder-related complications.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[00023] In accordance with the present invention, it has been discovered that otic disorders and otic disorder-related complications may be treated and prevented in a subject by administering to the subject a Cox-2 inhibitor alone or in combination with one or more otic agents.

[00024] For purposes of the present invention, the novel monotherapy or combination therapy comprising at least one Cox-2 inhibitor alone or in combination with at least one otic agent is also useful for the purpose of preventing and treating otic disorders and otic disorder-related complications in a subject that is in need of such prevention or treatment.

[00025] Thus, the monotherapy and combination therapy of the present invention would be useful, for example, to reduce such otic disorder symptoms as, for example, otic pain, inflammation, otorrhea, otalgia, fever, and otic bleeding in a subject suffering from such symptoms. The monotherapy or combination therapy of the present invention would also be useful to prevent the occurrence of such symptoms.

[00026] The methods and compositions of the present invention are also useful to reduce the number of hospitalizations of subjects suffering

from an otic disorder, or to prevent or retard, in subjects, the development of complications associated with otic disorders, such as, for example, hearing loss, brain abscess, meningitis and facial paralysis, which may eventually arise from having a chronic or recurring otic disorder.

[00027] The combination therapy of a Cox-2 inhibitor and an otic agent is also useful for decreasing the required number of separate dosages, thus, potentially improving patient compliance.

[00028] The administration of a Cox-2 inhibitor for the prevention and treatment of otic disorders and otic disorder-related complications is an unexpectedly effective treatment and preventative therapy. Such administration is effective for improving the symptoms of otic disorders and otic disorder-related complications while avoiding or reducing certain disadvantages of current treatments.

[00029] Furthermore, the administration of a Cox-2 inhibitor in combination with an otic agent is an effective treatment for otic disorders or otic disorder-related complications, and in preferred embodiments, is superior to the use of either agent alone. For example, the combination therapy is effective for lowering the dosages of otic agents that are normally prescribed as a monotherapy. The administration of lower dosages of conventional treatment agents provides a reduction in side effects corresponding to such conventional agents.

[00030] Combination therapies comprising Cox-2 inhibitors and otic agents are useful not only for improving otic disorder symptoms and shortening recovery times, but also for reducing the dosages of otic agents that are normally required.

[00031] Reduced dosages of otic agents are beneficial where normal dosages often exhibit harmful side effects, for example, with such otic agents as corticosteroids and antibiotics. Side effects from corticosteroid use can include osteoporosis, susceptibility to bruising, infections, diabetes, cataracts, glaucoma, high blood pressure and weight gain. Antibiotics may also produce unwanted side effects such as nausea, diarrhea and rashes.

[00032] As used herein, the phrases "combination therapy", "co-administration", "co-administering", "administration with", "administering", "combination", or "co-therapy", when referring to use of a Cox-2 inhibitor in combination with an otic agent, are intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner. Thus, the Cox-2 inhibitor and otic agent may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00033] Sequential administration of such treatments encompasses both relatively short and relatively long periods between the administration of each of the drugs of the present method. However, for purposes of the present invention, the second drug is administered while the first drug is still having an efficacious effect on the subject. Thus, the present invention, in one embodiment, takes advantage of the fact that the simultaneous presence of the combination of a Cox-2 inhibitor and an otic agent in a subject has a greater efficacy than the administration of either agent alone.

[00034] Preferably, the second of the two drugs is to be given to the subject within the therapeutic response time of the first drug to be administered. For example, the present invention encompasses administration of a Cox-2 inhibitor to the subject and the later administration of an otic agent, as long as the otic agent is administered to the subject while the Cox-2 inhibitor is still present in the subject at a level, which in combination with the level of the otic agent is therapeutically effective, and vice versa.

[00035] As used herein, the terms "therapeutic response time" mean the duration of time that a compound is present or detectable within a subject's body at therapeutic concentrations.

[00036] As used herein, the term "monotherapy" is intended to embrace administration of a Cox-2 inhibitor to a subject suffering from an otic disorders or otic disorder-related complication as a single therapeutic treatment without an additional therapeutic treatment comprising an otic agent. However, the Cox-2 inhibitor may still be administered in multiple dosage forms. Thus, the Cox-2 inhibitor may be administered in one therapeutic dosage form, such as in a single capsule, tablet, or injection, or in two separate therapeutic dosage forms, such as in separate capsules, tablets, or injections.

[00037] In one embodiment, the present invention encompasses a method for preventing an otic disorder in a subject, the method comprising administering to the subject a Cox-2 inhibitor alone or in combination with an otic agent.

[00038] As used herein, the terms "to prevent", "preventing", or "prevention" refer to any reduction, no matter how slight, of a subject's predisposition or risk for developing an otic disorder or an otic disorder-related complication. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing an otic disorder or an otic disorder-related complication. The term "prevention" includes either preventing the onset of a clinically evident otic disrder altogether or preventing the onset of a preclinically evident otic disorder in individuals at risk.

[00039] In another embodiment, the present invention encompasses a method for treating an otic disorder or an otic disorder-related complication in a subject, the method comprising administering to the subject a Cox-2 inhibitor alone or in combination with an otic agent.

[00040] As used herein, the terms "treating", "treatment", "treated", or "to treat," mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to alter or slow the appearance of symptoms or symptom worsening. The term "treatment" includes alleviation or elimination of causation of symtoms associated with, but not

limited to, any of the otic disorders or otic disorder related-complications described herein.

[00041] Without being bound by this or any other theory, it is believed that a therapy comprising a Cox-2 inhibitor is efficacious for impairing the process of inflammation within the ear, thus preventing or treating otic disorders and thereby otic disorder-related complications. Moreover, in preferred embodiments, the combination of a Cox-2 inhibitor and an otic agent provide synergistic effects, which reduces the symptoms associated with otic disorders and otic disorder-related complications to a greater extent than would be expected on the basis of the use of either one alone. The term "synergistic" refers to the combination of a Cox-2 inhibitor and an otic agent as a combined therapy having an efficacy for the prevention and treatment of otic disorders that is greater than the sum of their individual effects.

[00042] The synergistic effects of preferred embodiments of the present invention's combination therapy encompass additional unexpected advantages for the treatment and prevention of otic disorders. Such additional advantages include, but are not limited to, lowering the required dose of otic agents, reducing the side-effects of otic agents, and rendering those agents more tolerable to subjects undergoing otic disorder therapy.

[00043] Also, the monotherapy and combination therapy of the present invention provide for the treatment of otic disorder-related complications, which may arise indirectly from having an otic disorder, by treating the underlying otic disorder itself. For example, if a subject is suffering from an otic disorder-related complication, such as temporary hearing loss, the treatment of the underlying otic disorder, such as otitis media, by the methods and compositions of the present invention will likewise improve the symptoms of the associated complication.

[00044] The present invention is directed to a novel method of preventing or treating otic disorders and otic disorder-related complications in a subject that is in need of such prevention or treatment comprising administering to the subject a Cox-2 inhibitor.

[00045] The present invention is also directed to a novel method of preventing or treating otic disorders and otic disorder-related complications in a subject that is in need of such prevention or treatment comprising administering to the subject a Cox-2 inhibitor and one or more otic agents.

[00046] A component of the present invention is a Cox-2 inhibitor.

[00047] The terms "cyclooxygenase-2 inhibitor", or "Cox-2 inhibitor", which can be used interchangeably herein, embrace compounds which inhibit the Cox-2 enzyme regardless of the degree of inhibition of the Cox-1 enzyme, and include pharmaceutically acceptable salts of those compounds. Thus, for purposes of the present invention, a compound is considered a Cox-2 inhibitor irrespective of whether the compound inhibits the Cox-2 enzyme to an equal, greater, or lesser degree than the Cox-1 enzyme.

[00048] In one embodiment of the present invention, it is preferred that the Cox-2 inhibitor compound is a non-steroidal anti-inflammatory drug (NSAID). Therefore, preferred materials that can serve as the Cox-2 inhibitor of the present invention include non-steroidal anti-inflammatory drug compounds, a pharmaceutically acceptable salt thereof, or a pure (-) or (+) optical isomeric form thereof.

[00049] Examples of NSAID compounds that are useful in the present invention include acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, carprofen, choline magnesium trisalicylate, clidanac, clopinac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenec, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, feprazone, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, miroprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxipinac, oxyphenbutazone, phenylbutazone, podophyllotoxin derivatives, proglumetacin, piprofen, pirprofen, prapoprofen, salicylic acid, salicylate, sudoxicam, suprofen, sulindac,

tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, tolfenamic acid, tolmetin, zidometacin, zomepirac, and 2-fluoro-a-methyl[1,1'-biphenyl]-4-acetic acid, 4-(nitrooxy)butyl ester.

[00050] Further preferred NSAID compounds include ibuprofen, naproxen, sulindac, ketoporfen, fenoprofen, tiaprofenic acid, suprofen, etodolac, carprofen, ketrolac, piprofen, indoprofen, salicylic acid, and flurbiprofen.

[00051] In a preferred embodiment, the Cox-2 inhibitor is a Cox-2 selective inhibitor. The term "Cox-2 selective inhibitor" embraces compounds, which selectively inhibit the Cox-2 enzyme over the Cox-1 enzyme, and also include pharmaceutically acceptable salts and prodrugs of those compounds.

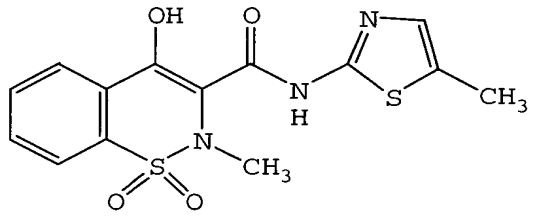
[00052] In practice, the selectivity of a Cox-2 inhibitor varies depending upon the condition under which the test is performed and on the inhibitors being tested. However, for the purposes of this specification, the selectivity of a Cox-2 inhibitor can be measured as a ratio of the *in vitro* or *in vivo* IC_{50} value for inhibition of Cox-1, divided by the IC_{50} value for inhibition of Cox-2 (Cox-1 IC_{50}/Cox-2 IC_{50}). A Cox-2 selective inhibitor is any inhibitor for which the ratio of Cox-1 IC_{50} to Cox-2 IC_{50} is greater than 1. In preferred embodiments, this ratio is greater than 2, more preferably greater than 5, yet more preferably greater than 10, still more preferably greater than 50, and more preferably still greater than 100.

[00053] As used herein, the term "IC_{50}" refers to the concentration of a compound that is required to produce 50% inhibition of cyclooxygenase activity. Preferred Cox-2 selective inhibitors of the present invention have a Cox-2 IC_{50} of less than about 1 μM, more preferred of less than about 0.5 μM, and even more preferred of less than about 0.2 μM.

[00054] Preferred Cox-2 selective inhibitors have a Cox-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

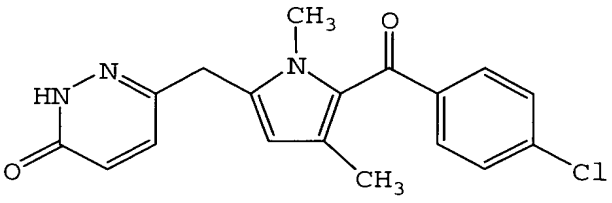
[00055] Also included within the scope of the present invention are compounds that act as prodrugs of Cox-2-selective inhibitors. As used herein in reference to Cox-2 selective inhibitors, the term "prodrug" refers to a chemical compound that can be converted into an active Cox-2 selective inhibitor by metabolic or simple chemical processes within the body of the subject. One example of a prodrug for a Cox-2 selective inhibitor is parecoxib, which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor valdecoxib. An example of a preferred Cox-2 selective inhibitor prodrug is sodium parecoxib. A class of prodrugs of Cox-2 inhibitors is described in U.S. Patent No. 5,932,598.

[00056] The Cox-2 selective inhibitor of the present invention can be, for example, the Cox-2 selective inhibitor meloxicam, Formula B-1 (CAS registry number 71125-38-7), or a pharmaceutically acceptable salt or prodrug thereof.



B-1

[00057] In another embodiment of the invention the Cox-2 selective inhibitor can be the Cox-2 selective inhibitor RS 57067, 6-[[5-(4-chlorobenzoyl)-1,4-dimethyl-1H-pyrrol-2-yl]methyl]-3(2H)-pyridazinone, Formula B-2 (CAS registry number 179382-91-3), or a pharmaceutically acceptable salt or prodrug thereof.



B-2

[00058] As used herein, the term "alkyl", either alone or within other terms such as "haloalkyl" and "alkylsulfonyl"; embraces linear or branched radicals having one to about twenty carbon atoms. Lower alkyl radicals have one to about ten carbon atoms. The number of carbon atoms can also be expressed as "C_1-C_5", for example. Examples of lower alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the, like.

[00059] The term "alkenyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains at least one double bond. The alkenyl radicals may be optionally substituted with groups such as those defined below. Examples of suitable alkenyl radicals include propenyl, 2-chloropropylenyl, buten-1yl, isobutenyl, penten-1yl, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexen-1-yl, 3-hydroxyhexen-1-yl, hepten-1-yl, octen-1-yl, and the like.

[00060] The term "alkynyl" refers to an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, such radicals preferably containing 2 to about 6 carbon atoms, more preferably from 2 to about 3 carbon atoms. The alkynyl radicals may be optionally substituted with groups such as described below. Examples of suitable alkynyl radicals include ethynyl, proynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals, and the like.

[00061] The term "oxo" means a single double-bonded oxygen.

[00062] The terms "hydrido", "-H", or "hydrogen", denote a single hydrogen atom (H). This hydrido radical may be attached, for example, to an oxygen atom to form a hydroxyl radical, or two hydrido radicals may be attached to a carbon atom to form a methylene (-CH_2 -) radical.

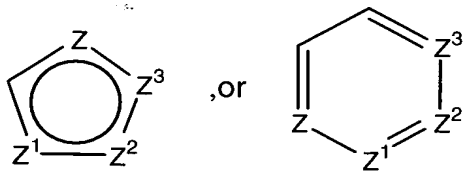
[00063] The term "halo" means halogens such as fluorine, chlorine, and bromine or iodine atoms. The term "haloalkyl" embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. Specifically embraced are monohaloalkyl, dihaloalkyl,

and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have a bromo, chloro, or a fluoro atom within the radical. Dihalo alkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals and polyhaloalkyl radicals may have more than two of the same halo atoms or a combination of different halo radicals.

[00064] The term "hydroxyalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more hydroxyl radicals.

[00065] The terms "alkoxy" and "alkoxyalkyl" embrace linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as methoxy radical. The term "alkoxyalkyl" also embraces alkyl radicals having two or more alkoxy radicals attached to the alkyl radical, that is, to form monoalkoxyalkyl and diaikoxyalkyl radicals. The "alkoxy" or "alkoxyalkyl" radicals may be further substituted with one or more halo atoms, such as fluoro, chloro, or bromo, to provide "haloalkoxy" or "haloalkoxyalkyl" radicals. Examples of "alkoxy" radicals include methoxy, butoxy, and trifluoromethoxy.

[00066] The term "aryl", whether used alone or with other terms, means a carbocyclic aromatic system containing one, two, or three rings wherein such rings may be attached together in a pendent manner, or may be fused. The term "aryl" embraces aromatic radicals such as phenyl, naphthyl, tetrahydronapthyl, indane, and biphenyl. The term "heterocyclyl" means a saturated or unsaturated mono- or multi-ring carbocycle wherein one or more carbon atoms are replaced by N, S, P, or O. This includes, for example, structures such as:



where Z, Z^1, Z^2, or Z^3 is C, S, P, O, or N, with the proviso that one of Z, Z^1, Z^2, or Z^3 is other than carbon, but is not O or S when attached to another Z atom by a double bond or when attached to another O or S atom. Furthermore, the optional substituents are understood to be attached to Z, Z^1, Z^2, or Z^3 only when each is C. The term "heterocycle" also includes fully saturated ring structures, such as piperazinyl, dioxanyl, tetrahydrofuranyl, oxiranyl, aziridinyl, morpholinyl, pyrrolidinyl, piperidinyl, thiazolidinyl, and others.

[00067] The term "heteroaryl" embraces unsaturated heterocyclic radicals. Examples of unsaturated heterocyclic radicals include thienyl, pyrryl, furyl, pyridyl, pyrimidyl, pyrazinyl, pyrazolyl, oxazolyl, isoxazolyl, imidazolyl, thiazolyl, pyranyl, and tetrazolyl. The term also embraces radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like.

[00068] The term "sulfonyl", whether used alone or linked to other terms such as alkylsulfonyl, denotes respectively divalent radicals $-SO_2-$. "Alkylsulfonyl", embraces alkyl radicals attached to a sulfonyl radical, where alkyl is defined as above. The term "arylsulfonyl" embraces sulfonyl radicals substituted with an aryl radical. The term "aminosulfonyl"denotes a sulfonyl radical substituted with an amine radical, forming a sulfonamide ($-SO_2$-NH_2).

[00069] The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes $-CO_2$-H. The term "carboxyalkyl" embraces radicals having a carboxyradical as defined above, attached to an alkyl radical. The term "carbonyl", whether used alone or with other terms, such as "alkylcarbonyl", denotes – (C=O) –. The term "alkylcarbonyl" embraces radicals having a carbonyl radical substituted with an alkyl radical. An example of an "alkylcarbonyl" radical is CH_3 – (CO) –. The term "alkoxycarbonyl" means a radical containing an alkoxy radical, as defined above, attached via an oxygen atom to a carbonyl (C=O) radical. Examples of such "alkoxycarbonyl" radicals

include $(CH_3)_3$-C-O–C=O) – and – (O=)C– OCH_3. The term "amino", whether used alone or with other terms, such as "aminocarbonyl", denotes $–NH_2$.

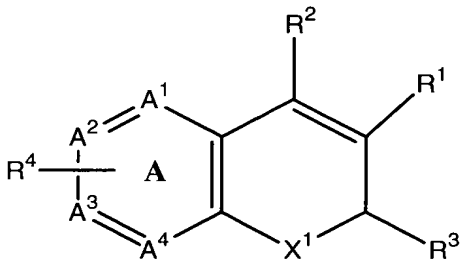
[00070] The term "heterocycloalkyl" embraces heterocyclic-substituted alkyl radicals such as pyridylmethyl and thienylmethyl. The terms "aralkyl", or "arylalkyl" embrace aryl-substituted alkyl radicals such as benzyl, diphenylmethyl, triphenylmethyl, phenylethyl, and diphenylethyl. The terms benzyl and phenylmethyl are interchangeable. The term "cycloalkyl" embraces radicals having three to ten carbon atoms, such as cyclopropyl cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl. The term "cycloalkenyl" embraces unsaturated radicals having three to ten carbon atoms, such as cylopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, and cycloheptenyl.

[00071] The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH_3 –S–). The term "alkylsulfinyl" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon atoms, attached to a divalent –S(–O) – atom. The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from an organic acid.

[00072] The term "cyano", used either alone or with other terms, such as "cyanoalkyl", refers to C≡N. The term "nitro" denotes $–NO_2$.

[00073] In one embodiment of the invention, the Cox-2 selective inhibitor is of the chromene/chroman structural class, which encompasses substituted benzopyrans or substituted benzopyran analogs, as well as substituted benzothiopyrans, dihydroquinolines, or dihydronaphthalenes having the structure of any one of the general Formulas I, II, III, IV, V, and VI, shown below, and including, by way of non-limiting example, the structures disclosed in Table 1, and the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

[00074] Benzopyrans that can serve as a Cox-2 selective inhibitor of the present invention include substituted benzopyran derivatives that are described in U.S. Patent Nos. 6,271,253 and 6,492,390. One such class of compounds is defined by the general formula shown below in formula **I**:



I

wherein X^1 is selected from O, S, $CR^c R^b$ and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl; or wherein $CR^b R^c$ forms a 3-6 membered cycloalkyl ring;

wherein R^1 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^2 is selected from hydrido, phenyl, thienyl, C_1 –C_6 –alkyl and C_2 –C_6 –alkenyl;

wherein R^3 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^4 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio,

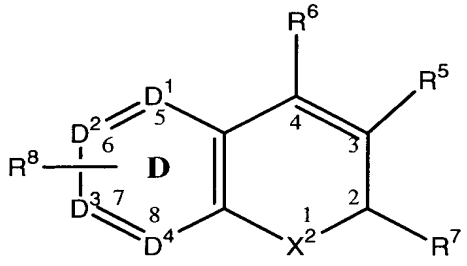
C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-$_1$ – C_3 –hydroxyalkyl, C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 – C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 – C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 – alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_1 –alkoxycarbonyl, formyl, C_1 –C_6 – haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the A ring atoms A^1, A^2, A^3 and A^4 are independently selected from carbon and nitrogen with the proviso that at least two of A^1, A^2, A^3 and A^4 are carbon;

or wherein R^4 together with ring A forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;

or an isomer or pharmaceutically acceptable salt thereof.

[00075] Another class of benzopyran derivatives that can serve as the Cox-2 selective inhibitor of the present invention includes compounds having the structure of formula **II**:



II

wherein X^2 is selected from O, S, CR^c R^b and NR^a ;

wherein R^a is selected from hydrido, C_1 –C_3 –alkyl, (optionally substituted phenyl)-C_1 –C_3 –alkyl, alkylsulfonyl, phenylsulfonyl, benzylsulfonyl, acyl and carboxy-C_1 –C_6 –alkyl;

wherein each of R^b and R^c is independently selected from hydrido, C_1 –C_3 –alkyl, phenyl-C_1 –C_3 –alkyl, C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

or wherein CR^c R^b form a cyclopropyl ring;

wherein R^5 is selected from carboxyl, aminocarbonyl, C_1 –C_6 –alkylsulfonylaminocarbonyl and C_1 –C_6 –alkoxycarbonyl;

wherein R^6 is selected from hydrido, phenyl, thienyl, C_2 –C_6 –alkynyl and C_2 –C_6 –alkenyl;

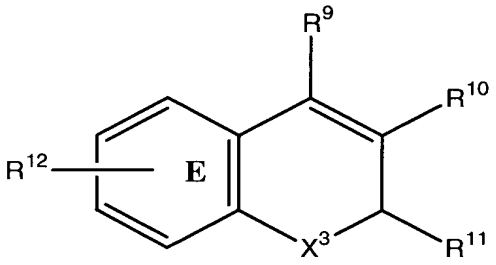
wherein R^7 is selected from C_1 –C_3 –perfluoroalkyl, chloro, C_1 –C_6 –alkylthio, C_1 –C_6 –alkoxy, nitro, cyano and cyano-C_1 –C_3 –alkyl;

wherein R^8 is one or more radicals independently selected from hydrido, halo, C_1 –C_6 –alkyl, C_2 –C_6 –alkenyl, C_2 –C_6 –alkynyl, halo-C_2 –C_6 –alkynyl, aryl-C_1 –C_3 –alkyl, aryl-C_2 –C_6 –alkynyl, aryl-C_2 –C_6 –alkenyl, C_1 –C_6 –alkoxy, methylenedioxy, C_1 –C_6 –alkylthio, C_1 –C_6 –alkylsulfinyl, —$O(CF_2)_2$ O—, aryloxy, arylthio, arylsulfinyl, heteroaryloxy, C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, aryl-C_1 –C_6 –alkyloxy, heteroaryl-C_1 –C_6 –alkyloxy, aryl-C_1 –C_6 –alkoxy-C_1 –C_6 –alkyl, C_1 –C_6 –haloalkyl, C_1 –C_6 –haloalkoxy, C_1 –C_6 –haloalkylthio, C_1 –C_6 –haloalkylsulfinyl, C_1 –C_6 –haloalkylsulfonyl, C_1 –C_3 –(haloalkyl-C_1 –C_3 –hydroxyalkyl), C_1 –C_6 –hydroxyalkyl, hydroxyimino-C_1 –C_6 –alkyl, C_1 –C_6 –alkylamino, arylamino, aryl-C_1 –C_6 –alkylamino, heteroarylamino, heteroaryl-C_1 –C_6 –alkylamino, nitro, cyano, amino, aminosulfonyl, C_1 –C_6 –alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aryl-C_1 –C_6 –alkylaminosulfonyl, heteroaryl-C_1 –C_6 –alkylaminosulfonyl, heterocyclylsulfonyl, C_1 –C_6 –alkylsulfonyl, aryl-C_1 –C_6 –alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aryl-C_1 –C_6 –alkylcarbonyl, heteroaryl-C_1 –C_6 –alkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, C_1 –C_6 –alkoxycarbonyl, formyl, C_1 –C_6 –haloalkylcarbonyl and C_1 –C_6 –alkylcarbonyl; and

wherein the D ring atoms D^1, D^2, D^3 and D^4 are independently selected from carbon and nitrogen with the proviso that at least two of D^1, D^2, D^3 and D^4 are carbon; or

wherein R^8 together with ring D forms a radical selected from naphthyl, quinolyl, isoquinolyl, quinolizinyl, quinoxalinyl and dibenzofuryl;
or an isomer or pharmaceutically acceptable salt thereof.

[00076] Other benzopyran Cox-2 selective inhibitors useful in the practice of the present invention are described in U.S. Patent Nos. 6,034,256 and 6,077,850. The general formula for these compounds is shown in formula **III**:

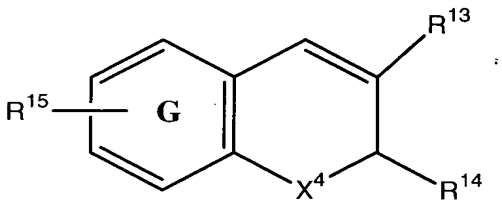


III

wherein X^3 is selected from the group consisting of O or S or NR^a;
wherein R^a is alkyl;
wherein R^9 is selected from the group consisting of H and aryl;
wherein R^{10} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;
wherein R^{11} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
wherein R^{12} is selected from the group consisting of one or more radicals selected from H, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl, nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or

wherein R^{12} together with ring E forms a naphthyl radical; or an isomer or pharmaceutically acceptable salt thereof; and
including the diastereomers, enantiomers, racemates, tautomers, salts, esters, amides and prodrugs thereof.

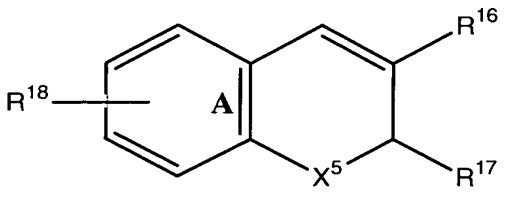
[00077] A related class of compounds useful as Cox-2 selective inhibitors in the present invention is described by Formulas **IV** and **V** below:



IV

wherein X^4 is selected from O or S or NR^a ;
wherein R^a is alkyl;
wherein R^{13} is selected from carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;
wherein R^{14} is selected from haloalkyl, alkyl, aralkyl, cycloalkyl and aryl optionally substituted with one or more radicals selected from alkylthio, nitro and alkylsulfonyl; and
wherein R^{15} is one or more radicals selected from hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl;
or wherein R^{15} together with ring G forms a naphthyl radical;
or an isomer or pharmaceutically acceptable salt thereof.

[00078] Formula **V** is:



V

wherein:

X^5 is selected from the group consisting of O or S or NR^b;

R^b is alkyl;

R^{16} is selected from the group consisting of carboxyl, aminocarbonyl, alkylsulfonylaminocarbonyl and alkoxycarbonyl;

R^{17} is selected from the group consisting of haloalkyl, alkyl, aralkyl, cycloalkyl and aryl, wherein haloalkyl, alkyl, aralkyl, cycloalkyl, and aryl each is independently optionally substituted with one or more radicals selected from the group consisting of alkylthio, nitro and alkylsulfonyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl, haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino, heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl, arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl, heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl, heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00079] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of lower haloalkyl, lower cycloalkyl and phenyl; and

R^{18} is one or more radicals selected from the group of consisting of hydrido, halo, lower alkyl, lower alkoxy, lower haloalkyl, lower haloalkoxy, lower alkylamino, nitro, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, lower alkylsulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or

wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00080] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is carboxyl;

R^{17} is lower haloalkyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkyl, lower haloalkoxy, lower alkylamino, amino, aminosulfonyl, lower alkylaminosulfonyl, 5-membered heteroarylalkylaminosulfonyl, 6-membered heteroarylalkylaminosulfonyl, lower aralkylaminosulfonyl, lower alkylsulfonyl, 6-membered nitrogen-containing heterocyclosulfonyl, optionally substituted phenyl, lower aralkylcarbonyl, and lower alkylcarbonyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00081] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting of fluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluoroethyl, difluoropropyl, dichloroethyl, dichloropropyl, difluoromethyl, and trifluoromethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, butyl, isobutyl, pentyl, hexyl, methoxy, ethoxy, isopropyloxy, tertbutyloxy, trifluoromethyl, difluoromethyl, trifluoromethoxy, amino, N,N-dimethylamino, N,N-diethylamino, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, nitro, N,N-dimethylaminosulfonyl, aminosulfonyl, N-methylaminosulfonyl, N-ethylsulfonyl, 2,2-dimethylethylaminosulfonyl, N,N-dimethylaminosulfonyl, N-(2-methylpropyl)aminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, 2,2-dimethylpropylcarbonyl, phenylacetyl and phenyl; or wherein R^2 together with ring A forms a naphthyl radical;

or an isomer or pharmaceutically acceptable salt thereof.

[00082] The Cox-2 selective inhibitor may also be a compound of Formula V, wherein:

X^5 is selected from the group consisting of oxygen and sulfur;

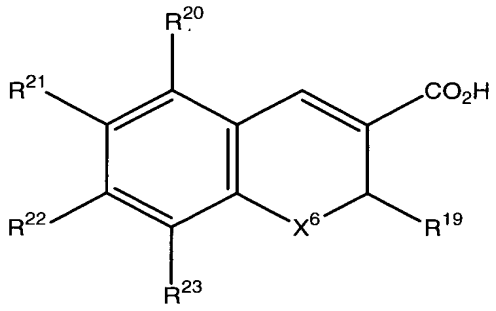
R^{16} is selected from the group consisting of carboxyl, lower alkyl, lower aralkyl and lower alkoxycarbonyl;

R^{17} is selected from the group consisting trifluoromethyl and pentafluoroethyl; and

R^{18} is one or more radicals selected from the group consisting of hydrido, chloro, fluoro, bromo, iodo, methyl, ethyl, isopropyl, *tert*-butyl, methoxy, trifluoromethyl, trifluoromethoxy, N-phenylmethylaminosulfonyl, N-phenylethylaminosulfonyl, N-(2-furylmethyl)aminosulfonyl, N,N-dimethylaminosulfonyl, N-methylaminosulfonyl, N-(2,2-dimethylethyl)aminosulfonyl, dimethylaminosulfonyl, 2-methylpropylaminosulfonyl, N-morpholinosulfonyl, methylsulfonyl, benzylcarbonyl, and phenyl; or wherein R^{18} together with ring A forms a naphthyl radical;

or an isomer or prodrug thereof.

[00083] The Cox-2 selective inhibitor of the present invention can also be a compound having the structure of Formula **VI**:



VI

wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is lower haloalkyl;

R^{20} is selected from the group consisting of hydrido, and halo;

R^{21} is selected from the group consisting of hydrido, halo, lower alkyl, lower haloalkoxy, lower alkoxy, lower aralkylcarbonyl, lower dialkylaminosulfonyl, lower alkylaminosulfonyl, lower aralkylaminosulfonyl, lower heteroaralkylaminosulfonyl, 5-membered nitrogen-containing heterocyclosulfonyl, and 6- membered nitrogen-containing heterocyclosulfonyl;

R^{22} is selected from the group consisting of hydrido, lower alkyl, halo, lower alkoxy, and aryl; and

R^{23} is selected from the group consisting of the group consisting of hydrido, halo, lower alkyl, lower alkoxy, and aryl;

or an isomer or prodrug thereof.

[00084] The Cox-2 selective inhibitor can also be a compound of having the structure of Formula VI, wherein:

X^6 is selected from the group consisting of O and S;

R^{19} is selected from the group consisting of trifluoromethyl and pentafluoroethyl;

R^{20} is selected from the group consisting of hydrido, chloro, and fluoro;

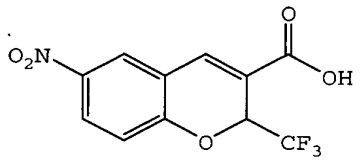
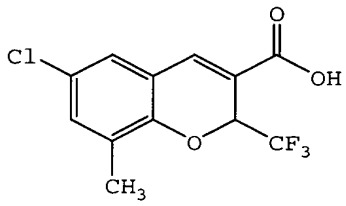
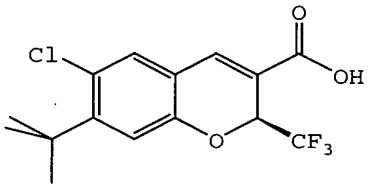
R^{21} is selected from the group consisting of hydrido, chloro, bromo, fluoro, iodo, methyl, tert-butyl, trifluoromethoxy, methoxy, benzylcarbonyl, dimethylaminosulfonyl, isopropylaminosulfonyl, methylaminosulfonyl, benzylaminosulfonyl, phenylethylaminosulfonyl, methylpropylaminosulfonyl, methylsulfonyl, and morpholinosulfonyl;

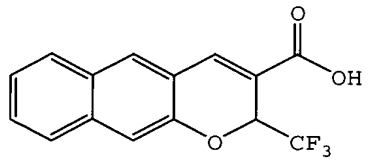
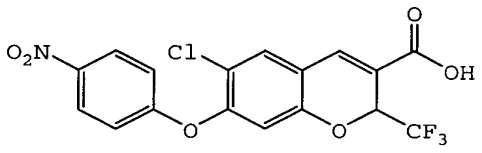
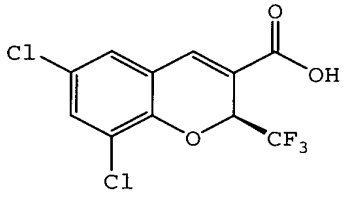
R^{22} is selected from the group consisting of hydrido, methyl, ethyl, isopropyl, tert-butyl, chloro, methoxy, diethylamino, and phenyl; and

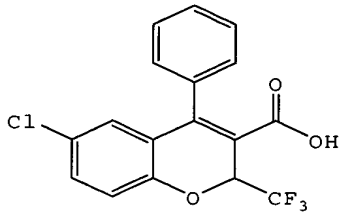
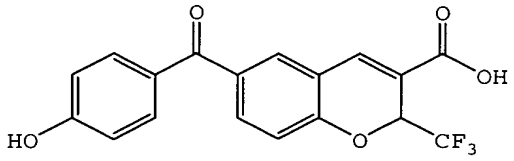
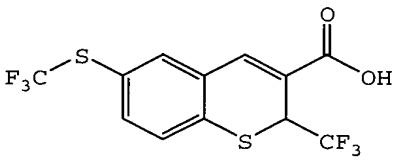
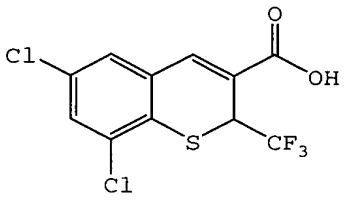
R^{23} is selected from the group consisting of hydrido, chloro, bromo, fluoro, methyl, ethyl, tert-butyl, methoxy, and phenyl;

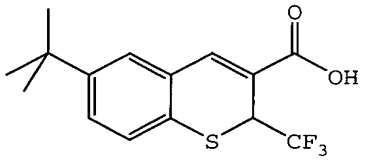
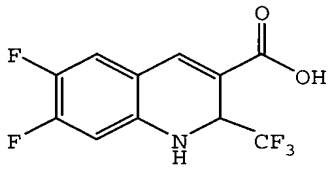
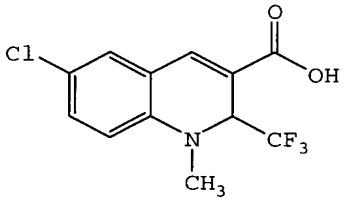
or an isomer or prodrug thereof.

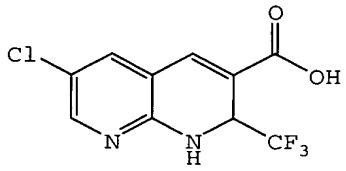
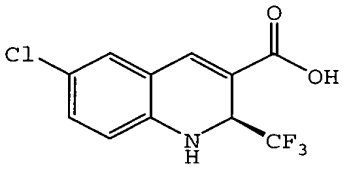
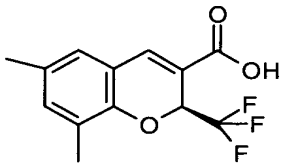
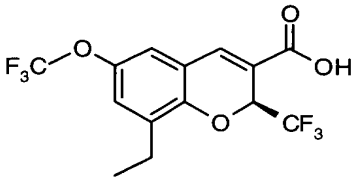
Table 1. Examples of Chromene Cox-2 Selective Inhibitors

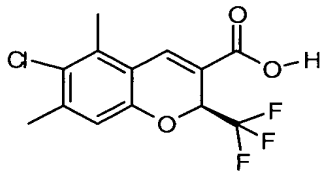
Compound Number	**Structural Formula**
B-3	 6-Nitro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-4	 6-Chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid
B-5	 ((S)-6-Chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-6	 2-Trifluoromethyl-2H-naphtho[2,3-b]pyran-3-carboxylic acid
B-7	 6-Chloro-7-(4-nitrophenoxy)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-8	 ((S)-6,8-Dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid

Compound Number	Structural Formula
B-9	 6-Chloro-2-(trifluoromethyl)-4-phenyl-2H-1-benzopyran-3-carboxylic acid
B-10	 6-(4-Hydroxybenzoyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid
B-11	 2-(Trifluoromethyl)-6-[(trifluoromethyl)thio]-2H-1-benzothiopyran-3-carboxylic acid
B-12	 6,8-Dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid

Compound Number	Structural Formula
B-13	 6-(1,1-Dimethylethyl)-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid
B-14	 6,7-Difluoro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-15	 6-Chloro-1,2-dihydro-1-methyl-2-(trifluoromethyl)-3-quinolinecarboxylic acid

Compound Number	Structural Formula
B-16	 6-Chloro-2-(trifluoromethyl)-1,2-dihydro[1,8]naphthyridine-3-carboxylic acid
B-17	 ((S)-6-Chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid
B-18	 (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid
B-19	 (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

Compound Number	Structural Formula
B-20	 (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid

[00085] In preferred embodiments, the chromene Cox-2 inhibitor is comprises at least one compound selected from the group consisting of 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid, 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid, 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

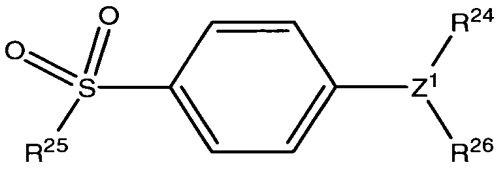
6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid,
6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,

6,8-dichloro-(S)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid.
6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6-formyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-(difluoromethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-7-methyl-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
(S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
(S)-6-chloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6,8-dichloro-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid,
5,6-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
2,6-bis(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,

5,6,7-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6,7,8-trichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid,
6-iodo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-bromo-1,2-dihydro-2-(trifluoromethyl)-3-quinolinecarboxylic acid,
6-chloro-7-methyl-2-(trifluoromethyl)-2H-1-benzothiopyran-3-carboxylic acid,
6,8-dichloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid, and mixtures thereof.

[00086] In further preferred embodiments, the chromene Cox-2 inhibitor is selected from (S)-6-chloro-7-(1,1-dimethylethyl)-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6,8-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-6-chloro-8-methyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (2S)-8-ethyl-6-(trifluoromethoxy)-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid, (2S)-6-chloro-5,7-dimethyl-2-(trifluoromethyl)-2H-chromene-3-carboxylic acid, and mixtures thereof.

[00087] In a preferred embodiment of the invention, the Cox-2 inhibitor can be selected from the class of tricyclic Cox-2 selective inhibitors represented by the general structure of formula **VII**:



VII

wherein:

Z^1 is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R^{24} is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R^{24} is optionally substituted at a

substitutable position with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R^{25} is selected from the group consisting of methyl or amino; and

R^{26} is selected from the group consisting of a radical selected from H, halo, alkyl, alkenyl, alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocyclyloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxycarbonyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxycarbonylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, N-alkyl-N-arylaminosulfonyl;

or a prodrug thereof.

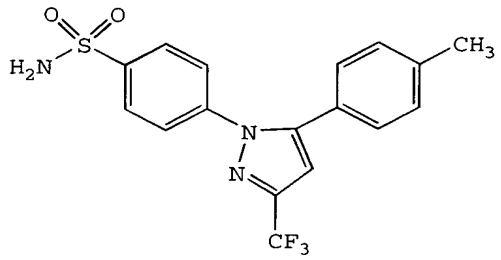
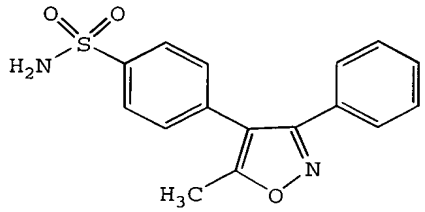
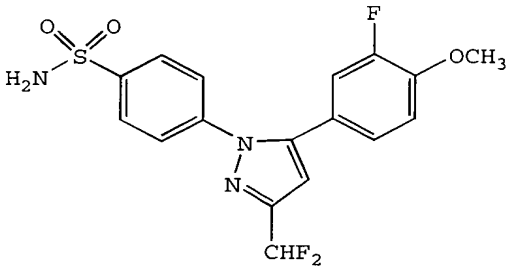
[00088] In a preferred embodiment of the invention, the tricyclic Cox-2 selective inhibitor comprises at least one compound selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

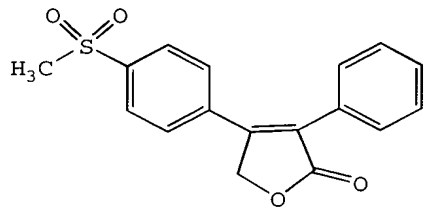
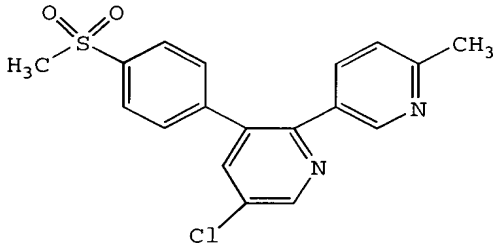
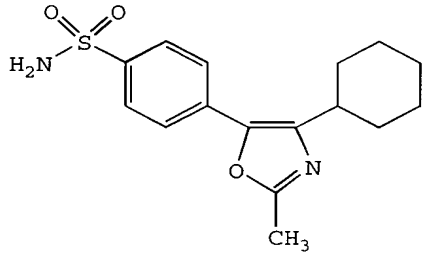
[00089] In a further preferred embodiment of the invention, the Cox-2 selective inhibitor represented by the above Formula VII is selected from the group of compounds, illustrated in Table 2, which includes celecoxib (B-21), valdecoxib (B-22), deracoxib (B-23), rofecoxib (B-24), etoricoxib (MK-663; B-25), JTE-522 (B-26), or prodrugs thereof.

[00090] Additional information about selected examples of the Cox-2 selective inhibitors discussed above can be found as follows: celecoxib

(CAS RN 169590-42-5, C-2779, SC-58653, and in U.S. Patent No. 5,466,823); deracoxib (CAS RN 169590-41-4); rofecoxib (CAS RN 162011-90-7); compound B-24 (U.S. Patent No. 5,840,924); compound B-26 (WO 00/25779); and etoricoxib (CAS RN 202409-33-4, MK-663, SC-86218, and in WO 98/03484).

Table 2. Examples of Tricyclic Cox-2 Selective Inhibitors

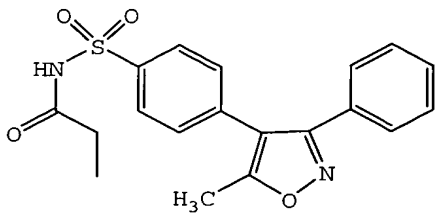
Compound Number	**Structural Formula**
B-21	
B-22	
B-23	

Compound Number	Structural Formula
B-24	
B-25	
B-26	

[00091] In a more preferred embodiment of the invention, the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, rofecoxib and etoricoxib.

[00092] In a preferred embodiment, parecoxib (See, U.S. Patent No. 5,932,598), having the structure shown in B-27, and which is a therapeutically effective prodrug of the tricyclic Cox-2 selective inhibitor

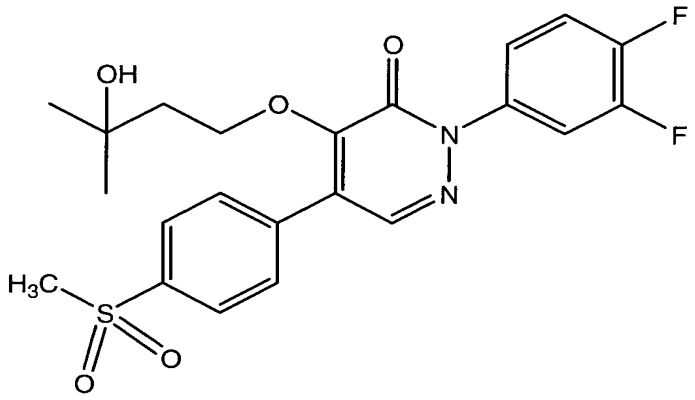
valdecoxib, B-22, (See, U.S. Patent No. 5,633,272), may be advantageously employed as the Cox-2 inhibitor of the present invention.



B-27

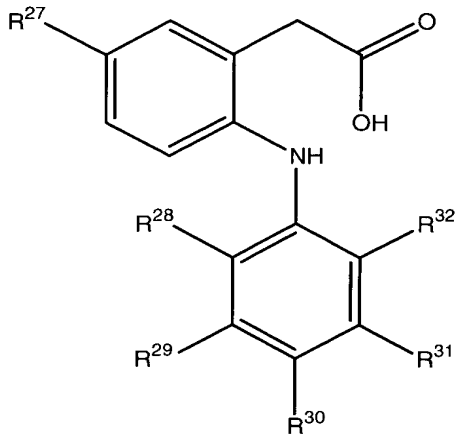
[00093] A preferred form of parecoxib is sodium parecoxib.

[00094] Another tricyclic Cox-2 selective inhibitor useful in the present invention is the compound ABT-963, having the formula B-28 shown below, that has been previously described in International Publication Number WO 00/24719.



B-28

[00095] In a further embodiment of the invention, the Cox-2 inhibitor can be selected from the class of phenylacetic acid derivative Cox-2 selective inhibitors represented by the general structure of formula **VIII**:



VIII

wherein:

R^{27} is methyl, ethyl, or propyl;

R^{28} is chloro or fluoro;

R^{29} is hydrogen, fluoro, or methyl;

R^{30} is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or hydroxyl;

R^{31} is hydrogen, fluoro, or methyl; and

R^{32} is chloro, fluoro, trifluoromethyl, methyl, or ethyl,

provided that R^{28}, R^{29}, R^{30} and R^{31} are not all fluoro when R^{27} is ethyl and R^{30} is H.

[00096] An exemplary phenylacetic acid derivative Cox-2 selective inhibitor that is described in WO 99/11605 is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is ethyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are hydrogen; and

R^{32} is methyl.

[00097] Another phenylacetic acid derivative Cox-2 selective inhibitor is a compound that has the structure shown in formula **VIII**,

wherein:

R^{27} is propyl;

R^{28} and R^{30} are chloro;

R^{29} and R^{31} are methyl; and

R^{32} is ethyl.

[00098] Another phenylacetic acid derivative Cox-2 selective inhibitor that is disclosed in WO 02/20090 is a compound that is referred to as COX-189 (also termed lumiracoxib; CAS Reg. No. 220991-20-8), having the structure shown in formula **VIII**,

wherein:

R^{27} is methyl;

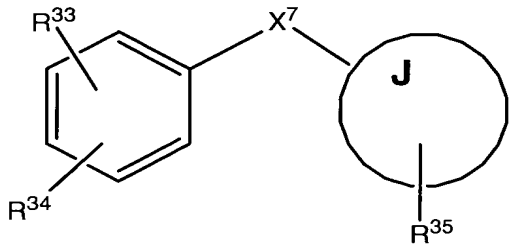
R^{28} is fluoro;

R^{32} is chloro; and

R^{29}, R^{30}, and R^{31} are hydrogen.

[00099] Compounds having a structure similar to that shown in formula **VIII**, that can serve as the Cox-2 selective inhibitor of the present invention, are described in U.S. Patent Nos. 6,451,858, 6,310,099, 6,291,523, and 5,958,978.

[000100] Other Cox-2 selective inhibitors that can be used in the present invention have the general structure shown in formula **IX**, where the J group is a carbocycle or a heterocycle. Preferred embodiments have the structure:



IX

wherein:

X^7 is O; J is 1-phenyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 4-NO_2; and there is no R^{35} group, (nimesulide), or

X^7 is O; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$NHSO_2CH_3$, (flosulide); or

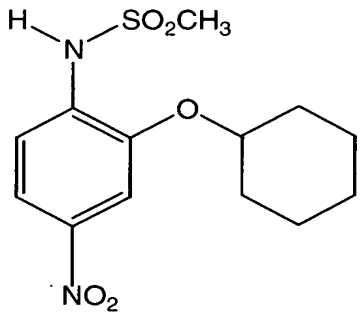
X^7 is O; J is cyclohexyl; R^{33} is 2-$NHSO_2CH_3$; R^{34} is 5-NO_2; and there is no R^{35} group, (NS-398); or

X^7 is S; J is 1-oxo-inden-5-yl; R^{33} is 2-F; R^{34} is 4-F; and R^{35} is 6-$N^-SO_2CH_3 \cdot Na^+$, (L-745337); or

X^7 is S; J is thiophen-2-yl; R^{33} is 4-F; there is no R^{34} group; and R^{35} is 5-$NHSO_2CH_3$, (RWJ-63556); or

X^7 is O; J is 2-oxo-5(R)-methyl-5-(2,2,2-trifluoroethyl)furan-(5H)-3-yl; R^{33} is 3-F; R^{34} is 4-F; and R^{35} is 4-(p-SO_2CH_3)C_6H_4, (L-784512).

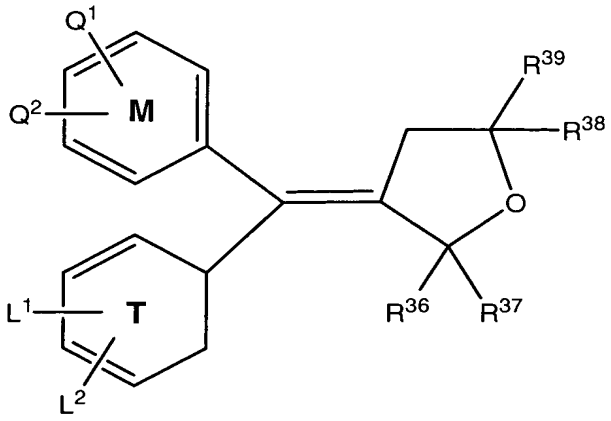
[000101] The Cox-2 selective inhibitor NS-398, also known as N-(2-cyclohexyloxynitrophenyl) methane sulfonamide (CAS RN 123653-11-2), having a structure as shown below in formula B-29, has been described in, for example, Yoshimi, N. *et al.,* in *Japanese J. Cancer Res., 90(4):*406 – 412 (1999).



B-29

[000102] An evaluation of the anti-inflammatory activity of the Cox-2 selective inhibitor, RWJ 63556, in a canine model of inflammation, was described by Kirchner *et al.,* in *J Pharmacol Exp Ther 282*, 1094-1101 (1997).

[000103] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylmethylidenefuran derivatives that are described in U.S. Patent No. 6,180,651. Such diarylmethylidenefuran derivatives have the general formula shown below in formula **X**:



X

wherein:

the rings T and M independently are a phenyl radical, a naphthyl radical, a radical derived from a heterocycle comprising 5 to 6 members and possessing from 1 to 4 heteroatoms, or a radical derived from a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

at least one of the substituents Q^1, Q^2, L^1 or L^2 is an $—S(O)_n—R$ group, in which n is an integer equal to 0, 1 or 2 and R is a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an $–SO_2NH_2$ group;

and is located in the para position,

the others independently being a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a trifluoromethyl radical, or a lower O-alkyl radical having 1 to 6 carbon atoms, or Q^1 and Q^2 or L^1 and L^2 are a methylenedioxy group; and

R^{36}, R^{37}, R^{38} and R^{39} independently are a hydrogen atom, a halogen atom, a lower alkyl radical having 1 to 6 carbon atoms, a lower haloalkyl radical having 1 to 6 carbon atoms, or an aromatic radical selected from the group consisting of phenyl, naphthyl, thienyl, furyl and pyridyl; or,

R^{36}, R^{37} or R^{38}, R^{39} are an oxygen atom; or

R^{36}, R^{37} or R^{38}, R^{39}, together with the carbon atom to which they are attached, form a saturated hydrocarbon ring having from 3 to 7 carbon atoms;

or an isomer or prodrug thereof.

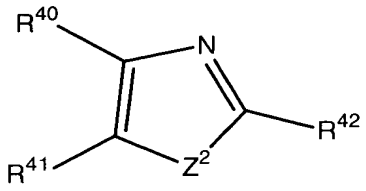
[000104] Particular diarylmethylidenefuran derivatives that can serve as the Cox-2 selective inhibitor of the present invention include, for example, N-(2-cyclohexyloxynitrophenyl)methane sulfonamide, and (E)-4-[(4-methylphenyl)(tetrahydro-2-oxo-3-furanylidene) methyl]benzenesulfonamide.

[000105] Other Cox-2 selective inhibitors that are useful in the present invention include darbufelone (Pfizer), CS-502 (Sankyo), LAS 34475 (Almirall Profesfarma), LAS 34555 (Almirall Profesfarma), S-33516 (Servier), SD 8381 (Pharmacia, described in U.S. Patent No. 6,034,256), BMS-347070 (Bristol Myers Squibb, described in U.S. Patent No. 6,180,651), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1367 (Chiroscience), L-748731 (Merck), CT3 (Atlantic Pharmaceutical), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), 6-dioxo-9H-purin-8-yl-cinnamic acid (Glaxo Wellcome), and S-2474 (Shionogi).

[000106] Compounds that may act as Cox-2 selective inhibitors of the present invention include multibinding compounds containing from 2 to 10 ligands covanlently attached to one or more linkers, as described in U.S. Patent No. 6,395,724.

[000107] Conjugated linoleic, as described in U.S. Patent No. 6,077,868, is useful as a Cox-2 selective inhibitor in the present invention.

[000108] Compounds that can serve as a Cox-2 selective inhibitor of the present invention include heterocyclic aromatic oxazole compounds that are described in U.S. Patents 5,994,381 and 6,362,209. Such heterocyclic aromatic oxazole compounds have the formula shown below in formula **XI**:

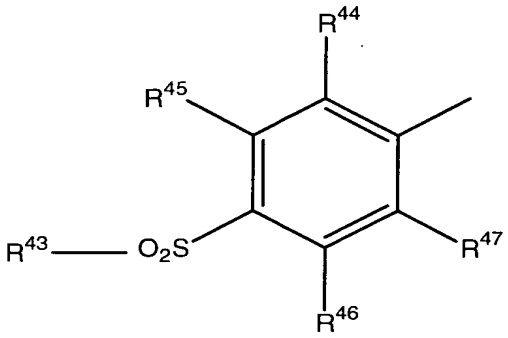


XI

wherein:

Z^2 is an oxygen atom;

one of R^{40} and R^{41} is a group of the formula



wherein:

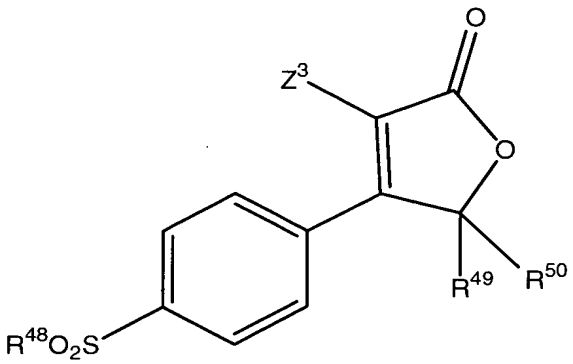
R^{43} is lower alkyl, amino or lower alkylamino; and

R^{44}, R^{45}, R^{46} and R^{47} are the same or different and each is hydrogen atom, halogen atom, lower alkyl, lower alkoxy, trifluoromethyl, hydroxyl or amino, provided that at least one of R^{44}, R^{45}, R^{46} and R^{47} is not hydrogen atom, and the other is an optionally substituted cycloalkyl, an optionally substituted heterocyclic group or an optionally substituted aryl; and

R^{30} is a lower alkyl or a halogenated lower alkyl,

and a pharmaceutically acceptable salt thereof.

[000109] Cox-2 selective inhibitors that are useful in the method and compositions of the present invention include compounds that are described in U.S. Patent Nos. 6,080,876 and 6,133,292, and described by formula **XII**:



XII

wherein:

Z^3 is selected from the group consisting of linear or branched C_1 –C_6 alkyl, linear or branched C_1 –C_6 alkoxy, unsubstituted, mono-, di- or tri-substituted phenyl or naphthyl wherein the substituents are selected from the group consisting of hydrogen, halo, C_1 –C_3 alkoxy, CN, C_1 –C_3 fluoroalkyl C_1 –C_3 alkyl, and –CO_2 H;

R^{48} is selected from the group consisting of NH_2 and CH_3,

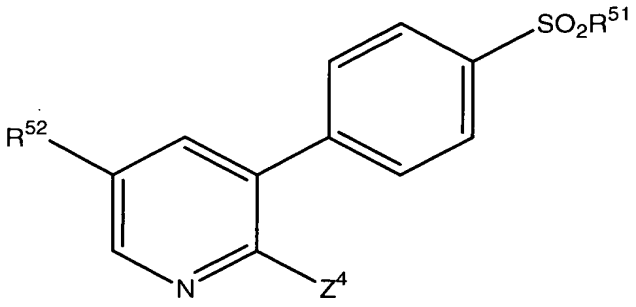
R^{49} is selected from the group consisting of C_1 –C_6 alkyl unsubstituted or substituted with C_3 –C_6 cycloalkyl, and C_3 –C_6 cycloalkyl;

R^{50} is selected from the group consisting of:

C_1 –C_6 alkyl unsubstituted or substituted with one, two or three fluoro atoms, and C_3 –C_6 cycloalkyl;

with the proviso that R^{49} and R^{50} are not the same.

[000110] Pyridines that are described in U.S. Patent Nos. 6,596,736, 6,369,275, 6,127,545, 6,130,334, 6,204,387, 6,071,936, 6,001,843 and 6,040,450, and can seve as Cox-2 selective inhibitors of the present invention, have the general formula described by formula **XIII**:



XIII

wherein:

R^{51} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

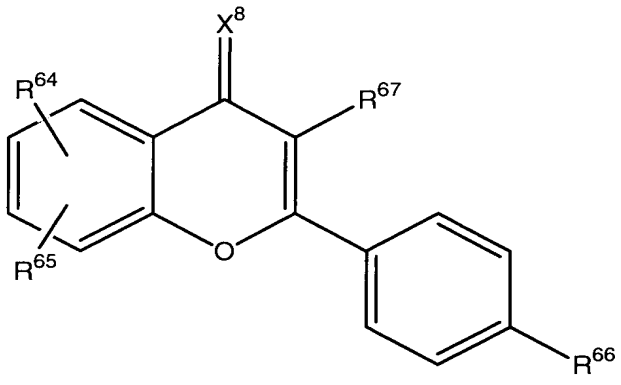
Z^4 is a mono-, di-, or trisubstituted phenyl or pyridinyl (or the N-oxide thereof), wherein the substituents are chosen from the group consisting of hydrogen, halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, $–CO_2R^{53}$, hydroxyl, $–C(R^{54})(R^{55})—OH$, – C_1 –C_6 alkyl-$CO_2—R^{56}$, C_1 –C_6 fluoroalkoxy;

R^{52} is chosen from the group consisting of: halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, $—CO_2R^{57}$, hydroxyl, $—C(R^{58})(R^{59})—OH$, — C_1 –C_6 alkyl-$CO_2—R^{60}$, C_1 –C_6 fluoroalkoxy, NO_2, $NR^{61}R^{62}$, and $NHCOR^{63}$;

R^{53}, R^{54}, R^{55}, R^{56}, R^{57}, R^{58}, R^{59}, R^{60}, R^{61}, R^{62}, and R^{63}, are each independently chosen from the group consisting of hydrogen andC_1 –C_6 alkyl;

or R^{54} and R^{55}, R^{58} and R^{59}, or R^{61} and R^{62} together with the atom to which they are attached form a saturated monocyclic ring of 3, 4, 5, 6, or 7 atoms.

[000111] Materials that can serve as the Cox-2 selective inhibitor of the present invention include diarylbenzopyran derivatives that are described in U.S. Patent No. 6,340,694. Such diarylbenzopyran derivatives have the general formula shown below in formula **XIV**:



XIV

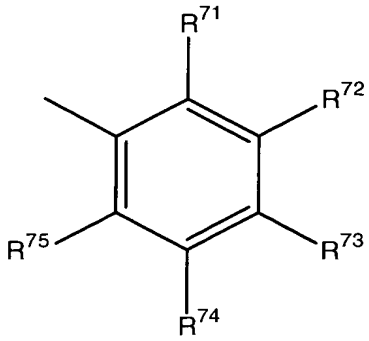
wherein:

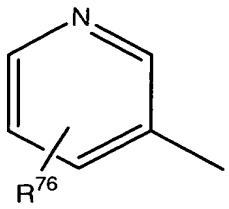
X^8 is an oxygen atom or a sulfur atom;

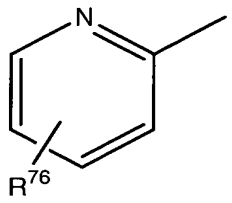
R^{64} and R^{65}, identical to or different from each other, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a nitro group, a nitrile group, or a carboxyl group;

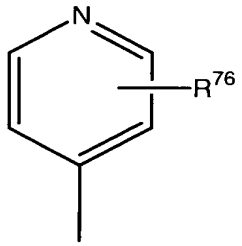
R^{66} is a group of a formula: $S(O)_nR^{68}$ wherein n is an integer of 0~2, R^{68} is a hydrogen atom, a C_1 –C_6 lower alkyl group, or a group of a formula: NR^{69} R^{70} wherein R^{69} and R^{70}, identical to or different from each other, are independently a hydrogen atom, or a C_1 –C_6 lower alkyl group; and

R^{67} is oxazolyl, benzo[b]thienyl, furanyl, thienyl, naphthyl, thiazolyl, indolyl, pyrolyl, benzofuranyl, pyrazolyl, pyrazolyl substituted with a C_1 –C_6 lower alkyl group, indanyl, pyrazinyl, or a substituted group represented by the following structures:









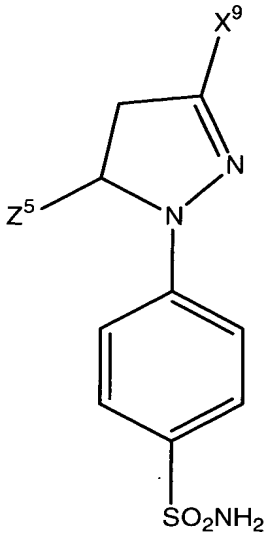
wherein:

R^{71} through R^{75}, identical to or different from one another, are independently a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a hydroxyalkyl group, a nitro group, a group of a formula: $S(O)_nR^{68}$, a group of a formula: NR^{69} R^{70}, a trifluoromethoxy group, a nitrile group a carboxyl group, an acetyl group, or a formyl group,

wherein n, R^{68}, R^{69} and R^{70} have the same meaning as defined by R^{66} above; and

R^{76} is a hydrogen atom, a halogen atom, a C_1 –C_6 lower alkyl group, a trifluoromethyl group, an alkoxy group, a hydroxyl group, a trifluoromethoxy group, a carboxyl group, or an acetyl group.

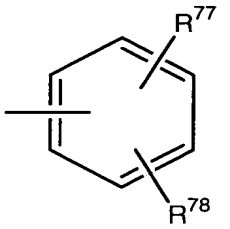
[000112] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines that are described in U.S. Patent No. 6,376,519. Such 1-(4-sulfamylaryl)-3-substituted-5-aryl-2-pyrazolines have the formula shown below in formula **XV**:



XV

wherein:

X^9 is selected from the group consisting of C_1 –C_6 trihalomethyl, preferably trifluoromethyl; C_1 –C_6 alkyl; and an optionally substituted or di-substituted phenyl group of formula **XVI**:



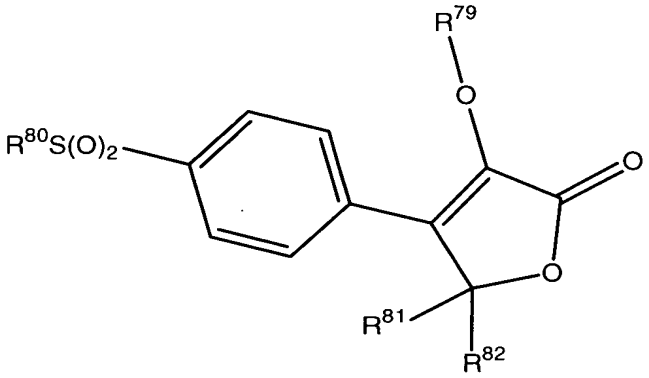
XVI

wherein:

R^{77} and R^{78} are independently selected from the group consisting of hydrogen, halogen, preferably chlorine, fluorine and bromine; hydroxyl; nitro; C_1 –C_6 alkyl, preferably C_1 –C_3 alkyl; C_1 –C_6 alkoxy, preferably C_1 – C_3 alkoxy; carboxy; C_1 –C_6 trihaloalkyl, preferably trihalomethyl, most preferably trifluoromethyl; and cyano;

Z^5 is selected from the group consisting of substituted and unsubstituted aryl.

[000113] Compounds useful as Cox-2 selective inhibitors of the present invention include heterocycles that are described in U.S. Patent No. 6,153,787. Such heterocycles have the general formulas shown below in formulas **XVII** and **XVIII**:



XVII

wherein:

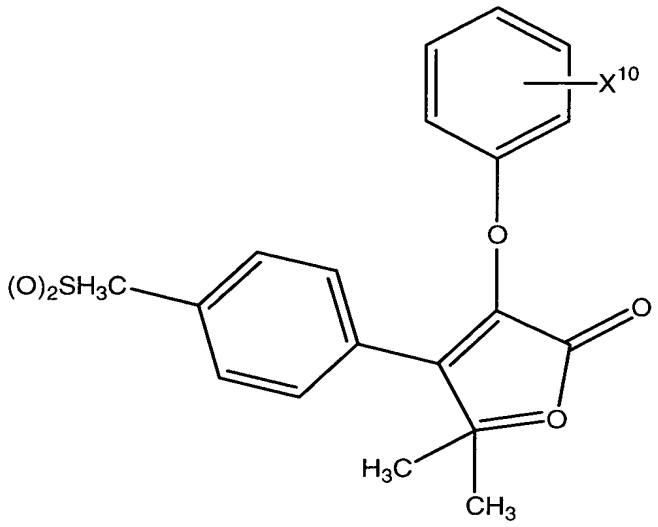
R^{79} is a mono-, di-, or tri-substituted C_1 –C_{12} alkyl, or a mono-, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkenyl, or an unsubstituted or mono-, di- or tri-substituted linear or branched C_2 –C_{10} alkynyl, or an unsubstituted or mono-, di- or tri-substituted C_3 –C_{12} cycloalkenyl, or an unsubstituted or mono-, di- or tri-substituted C_5 –C_{12} cycloalkynyl, wherein the substituents are chosen from the group consisting of halo selected from F, Cl, Br, and I, OH, CF_3, C_3 – C_6 cycloalkyl, =O,dioxolane, CN;

R^{80} is selected from the group consisting of CH_3, NH_2, $NHC(O)CF_3$, and $NHCH_3$;

R^{81} and R^{82} are independently chosen from the group consisting of hydrogen and C_1 –C_{10} alkyl;

or R^{81} and R^{82} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms.

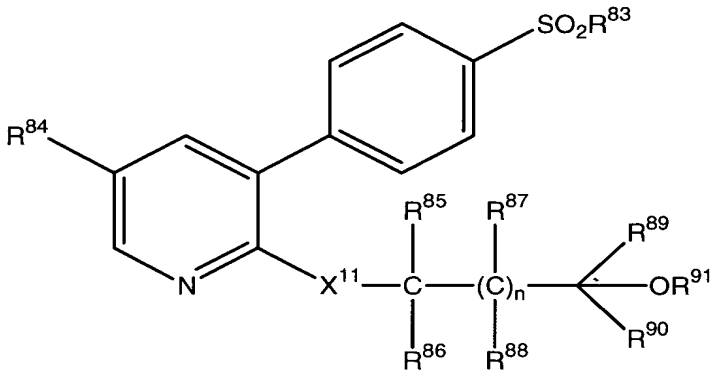
[000114] Formula **XVIII** is:



XVIII

wherein X^{10} is fluoro or chloro.

[000115] Materials that can serve as the Cox-2 selective inhibitor of the present invention include 2,3,5-trisubstituted pyridines that are described in U.S. Patent No. 6,046,217. Such pyridines have the general formula shown below in formula **XIX**:



XIX

or a pharmaceutically acceptable salt thereof,

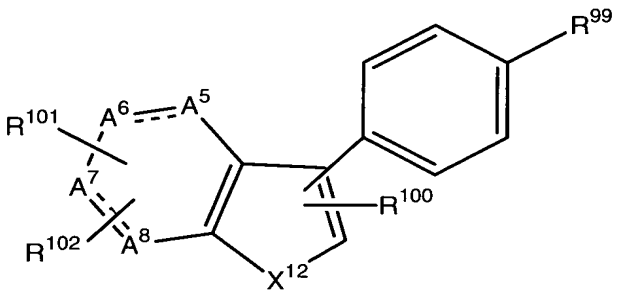
wherein:

X^{11} is selected from the group consisting of O, S, and a bond;

n is 0 or 1;

R^{83} is selected from the group consisting of CH_3, NH_2, and $NHC(O)CF_3$;
R^{84} is chosen from the group consisting of halo, C_1 –C_6 alkoxy, C_1 –C_6 alkylthio, CN, C_1 –C_6 alkyl, C_1 –C_6 fluoroalkyl, N_3, —CO_2 R^{92}, hydroxyl, —$C(R^{93})(R^{94})$—OH, —C_1 –C_6 alkyl-CO_2 —R^{95}, C_1 –C_6 fluoroalkoxy, NO_2, NR^{96} R^{97}, and $NHCOR^{98}$;
R^{85} to R^{89} are independently chosen from the group consisting of hydrogen and C_1 –C_6 alkyl;
or R^{85} and R^{89}, or R^{89} and R^{90} together with the atoms to which they are attached form a carbocyclic ring of 3, 4, 5, 6 or 7 atoms, or R^{85} and R^{87} are joined to form a bond.

[000116] Compounds that are useful as the Cox-2 selective inhibitor of the present invention include diaryl bicyclic heterocycles that are described in U.S. Patent No. 6,329,421. Such diaryl bicyclic heterocycles have the general formula shown below in formula **XX**:



XX

and pharmaceutically acceptable salts thereof wherein:
—A^5=A^6—A^7=A^8— is selected from the group consisting of:
(a) —CH=CH—CH=CH—,
(b) —CH_2 —CH_2 —CH_2 —C(O)—, —CH_2 —CH_2 —C(O)—CH_2 —, —CH_2 —C(O)—CH_2 —CH_2, —C(O)—CH_2 —CH_2 —CH_2,
(c) —CH_2 —CH_2 —C(O)—, —CH_2 —C(O)—CH_2 —, —C(O)—CH_2 —CH_2 —
(d) —CH_2 —CH_2 —O—C(O)—, CH_2 —O—C(O)—CH_2 —, —O—C(O)—CH_2 —CH_2 —,

(e) —CH_2 —CH_2 —C(O)—O—, —CH_2 —C(O)—OCH_2 —, —C(O)—O—CH_2 —CH_2 —,

(f) —$C(R^{105})_2$ —O—C(O)—, —C(O)—O—$C(R^{105})_2$ —, —O—C(O)—$C(R^{105})_2$ —, —$C(R^{105})_2$ —C(O)—O—,

(g) —N=CH—CH=CH—,

(h) —CH=N—CH=CH—,

(i) —CH=CH—N=CH—,

(j) —CH=CH—CH=N—,

(k) —N=CH—CH=N—,

(l) —N=CH—N=CH—,

(m) —CH=N—CH=N—,

(n) —S—CH=N—,

(o) —S—N=CH—,

(p) —N=N—NH—,

(q) —CH=N—S—, and

(r) —N=CH—S—;

R^{99} is selected from the group consisting of $S(O)_2CH_3$, $S(O)_2NH_2$, $S(O)_2NHCOCF_3$, $S(O)(NH)CH_3$, $S(O)(NH)NH_2$, $S(O)(NH)NHCOCF_3$, $P(O)(CH_3)OH$, and $P(O)(CH_3)NH_2$;

R^{100} is selected from the group consisting of:

(a) C_1 –C_6 alkyl,

(b) C_3 –C_7 cycloalkyl,

(c) mono- or di-substituted phenyl or naphthyl wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo, including F, Cl, Br, I,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —C(R^{103})(R^{104})—OH,

(12) —C(R^{103})(R^{104})—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{106};

(d) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additional N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —C(R^{103})(R^{104})—OH, and

(10) —C(R^{103})(R^{104})—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{101} and R^{102} are the substituents residing on any position of –A^5=A^6—A^7=A^8— and are selected independently from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) —Q^3 wherein Q^3 is Q^4, CO_2 H, C(R^{103})(R^{104})OH,

(f) —O—Q^4,

(g) —S—Q^4, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^3,

(2) —O—C_1 –C_5 alkyl-Q^3,

(3) —S—C_1 –C_5 alkyl-Q^3,

(4) —C_1 –C_3 alkyl-O—C_{1-3} alkyl-Q^3,

(5) —C_1 –C_3 alkyl-S—C_{1-3} alkyl-Q^3,

(6) —C_1 –C_5 alkyl-O—Q^4,

(7) —C_1 –C_5 alkyl-S—Q^4,

wherein the substituent resides on the alkyl chain and the substituent is C_1 –C_3 alkyl, and Q^3 is Q^4, CO_2 H, $C(R^{103})(R^{104})OH$ Q^4 is CO_2 —C_1 –C_4 alkyl, tetrazolyl-5-yl, or $C(R^{103})(R^{104})O$—C_1 –C_4 alkyl;

R^{103}, R^{104} and R^{105} are each independently selected from the group consisting of hydrogen and C_1 –C_6 alkyl; or

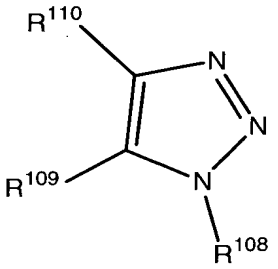
R^{103} and R^{104} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms, or two R^{105} groups on the same carbon form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

R^{106} is hydrogen or C_1 –C_6 alkyl;

R^{107} is hydrogen, C_1 –C_6 alkyl or aryl;

X^7 is O, S, NR^{107}, CO, $C(R^{107})_2$, $C(R^{107})(OH)$, —$C(R^{107})$=$C(R^{107})$—; —$C(R^{107})$=N—; or —N=$C(R^{107})$—.

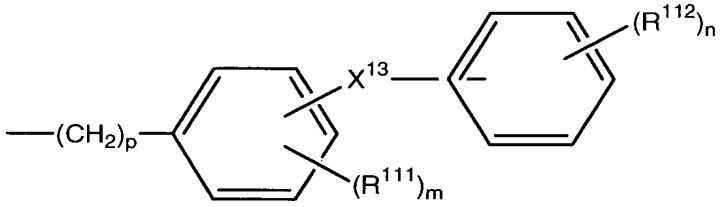
[000117] Compounds that may act as Cox-2 selective inhibitors include salts of 5-amino or a substituted amino 1,2,3-triazole compound that are described in U.S. Patent No. 6,239,137. The salts are of a class of compounds of formula **XXI**:



XXI

wherein:

R^{108} is:



wherein:

p is 0 to 2; m is 0 to 4; and n is 0 to 5;

X^{13} is O, S, SO, SO_2, CO, CHCN, CH_2 or $C=NR^{113}$ where R^{113} is hydrogen, loweralkyl, hydroxyl, loweralkoxy, amino, loweralkylamino, diloweralkylamino or cyano;

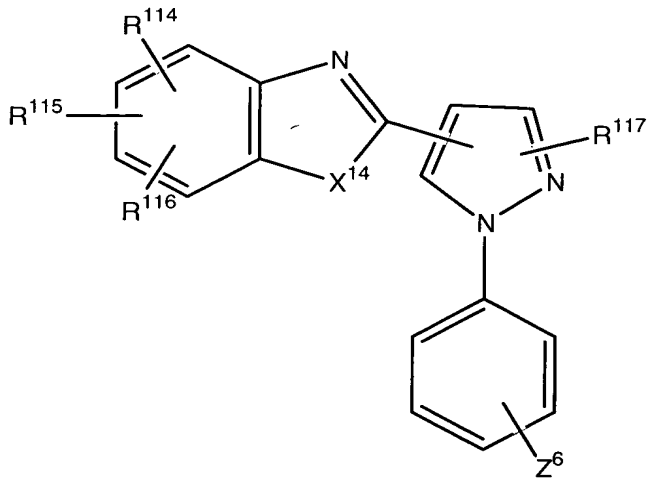
R^{111} and R^{112} are independently halogen, cyano, trifluoromethyl, loweralkanoyl, nitro, loweralkyl, loweralkoxy, carboxy, lowercarbalkoxy, trifuloromethoxy, acetamido, loweralkylthio, loweralkylsulfinyl, loweralkylsulfonyl, trichlorovinyl, trifluoromethylthio, trifluoromethylsulfinyl, or trifluoromethylsulfonyl;

R^{109} is amino, mono or diloweralkyl amino, acetamido, acetimido, ureido, formamido, or guanidino; and

R^{110} is carbamoyl, cyano, carbazoyl, amidino or N-hydroxycarbamoyl;

wherein the loweralkyl, loweralkyl containing, loweralkoxy and loweralkanoyl groups contain from 1 to 3 carbon atoms.

[000118] Pyrazole derivatives such as those described in U.S. Patent 6,136,831 can serve as a Cox-2 selective inhibitor of the present invention. Such pyrazole derivatives have the formula shown below in formula **XXII**:



XXII

wherein:

R^{114} is hydrogen or halogen;

R^{115} and R^{116} are each independently hydrogen, halogen, lower alkyl, lower alkoxy, hydroxyl or lower alkanoyloxy;

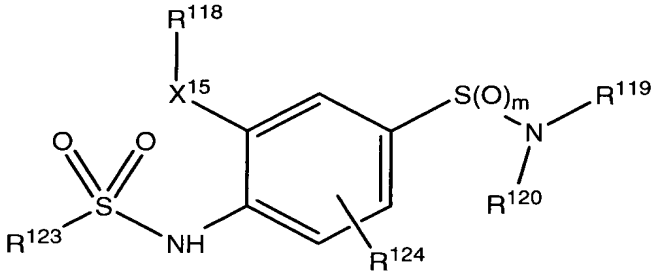
R^{117} is lower haloalkyl or lower alkyl;

X^{14} is sulfur, oxygen or NH; and

Z^6 is lower alkylthio, lower alkylsulfonyl or sulfamoyl;

or a pharmaceutically acceptable salt thereof.

[000119] Materials that can serve as a Cox-2 selective inhibitor of the present invention include substituted derivatives of benzosulphonamides that are described in U.S. Patent 6,297,282. Such benzosulphonamide derivatives have the formula shown below in formula **XXIII**:



XXIII

wherein:

X^{15} denotes oxygen, sulphur or NH;

R^{118} is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy;

R^{119} and R^{120}, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$ $-X^{16}$; or

R^{119} and R^{120}, together with the N- atom, denote a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$—X^{16};

X^{16} denotes halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121};

n denotes a whole number from 0 to 6;

R^{123} denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy;

R^{124} denotes halogen, hydroxyl, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, —OR^{121}, —COR^{121}, —CO_2 R^{121}, —OCO_2 R^{121}, —CN, —$CONR^{121}$ OR^{122}, —$CONR^{121}$ R^{122}, —SR^{121}, —$S(O)R^{121}$, —$S(O)_2$ R^{121}, —NR^{121} R^{122}, —$NHC(O)R^{121}$, —$NHS(O)_2$ R^{121}, or a polyfluoroalkyl group;

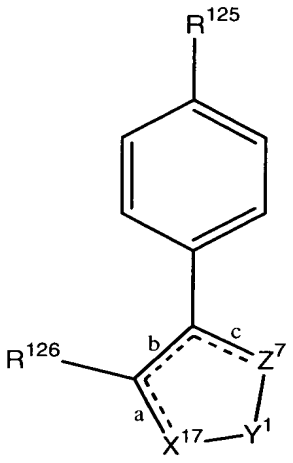
R^{121} and R^{122}, independently from one another, denote hydrogen, alkyl, aralkyl or aryl; and

m denotes a whole number from 0 to 2;

and the pharmaceutically-acceptable salts thereof.

[000120] Compounds that are useful as Cox-2 selective inhibitors of the present invention include phenyl heterocycles that are described in

U.S. Patent Nos. 5,474,995 and 6,239,173. Such phenyl heterocyclic compounds have the formula shown below in formula **XXIV**:



XXIV

or pharmaceutically acceptable salts thereof wherein:

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) —CH_2 CH_2 CH_2 —,

(b) —C(O)CH_2 CH_2 —,

(c) —CH_2 CH_2 C(O)—,

(d) —CR^{129} ($R^{129'}$)—O—C(O)—,

(e) —C(O)—O—CR^{129} ($R^{129'}$)—,

(f) —CH_2 —NR^{127} —CH_2 —,

(g) —CR^{129} ($R^{129'}$)—NR^{127} —C(O)—,

(h) —CR^{128}=$CR^{128'}$ —S—,

(i) —S—CR^{128}=$CR^{128'}$ —,

(j) —S—N=CH—,

(k) —CH=N—S—,

(l) —N=CR^{128} —O—,

(m) —O—CR^{128} =N— ,

(n) —N=CR^{128} —NH—,

(o) —N=CR^{128} —S—, and

(p) —S—CR^{128}=N—,

(q) —C(O)—NR^{127} —CR^{129} ($R^{129'}$)—,

(r) —R^{127} N—CH=CH— provided R^{122} is not —$S(O)_2CH_3$,

(s) —CH=CH—NR^{127} — provided R^{125} is not —$S(O)_2CH_3$;

when side b is a double bond, and sides a and c are single bonds; and

X^{17}—Y^1—Z^7-is selected from the group consisting of:

(a) =CH—O—CH=, and

(b) =CH—NR^{127} —CH=,

(c) =N—S—CH=,

(d) =CH—S—N=,

(e) =N—O—CH=,

(f) =CH—O—N=,

(g) =N—S—N=,

(h) =N—O—N=,

when sides a and c are double bonds and side b is a single bond;

R^{125} is selected from the group consisting of:

(a) $S(O)_2$ CH_3,

(b) $S(O)_2$ NH_2,

(c) $S(O)_2$ $NHC(O)CF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

(f) $S(O)(NH)NHC(O)CF_3$,

(g) $P(O)(CH_3)OH$, and

(h) $P(O)(CH_3)NH_2$;

R^{126} is selected from the group consisting of

(a) C_1 –C_6 alkyl,

(b) C_3, C_4, C_5, C_6, and C_7, cycloalkyl,

(c) mono-, di- or tri-substituted phenyl or naphthyl, wherein the substituent is selected from the group consisting of:

(1) hydrogen,

(2) halo,

(3) C_1 –C_6 alkoxy,

(4) C_1 –C_6 alkylthio,

(5) CN,

(6) CF_3,

(7) C_1 –C_6 alkyl,

(8) N_3,

(9) —CO_2 H,

(10) —CO_2 —C_1 –C_4 alkyl,

(11) —$C(R^{129})(R^{130})$—OH,

(12) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl, and

(13) —C_1 –C_6 alkyl-CO_2 —R^{129} ;

(d) mono-, di- or tri-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of:

(1) hydrogen,

(2) halo, including fluoro, chloro, bromo and iodo,

(3) C_1 –C_6 alkyl,

(4) C_1 –C_6 alkoxy,

(5) C_1 –C_6 alkylthio,

(6) CN,

(7) CF_3,

(8) N_3,

(9) —$C(R^{129})(R^{130})$—OH, and

(10) —$C(R^{129})(R^{130})$—O—C_1 –C_4 alkyl;

(e) benzoheteroaryl which includes the benzo fused analogs of (d);

R^{127} is selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) hydroxyl C_1 –C_6 alkyl,

(f) —C(O)— C_1 –C_6 alkyl,

(g) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —C_1 –C_5 alkyl-O—C_1 –C_3 alkyl-Q^5,

(3) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(4) —C_1 –C_5 alkyl-O—Q^5, or

(5) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl;

(h) –Q^5;

R^{128} and $R^{128'}$ are each independently selected from the group consisting of:

(a) hydrogen,

(b) CF_3,

(c) CN,

(d) C_1 –C_6 alkyl,

(e) –Q^5,

(f) —O—Q^5;

(g) —S—Q^5, and

(h) optionally substituted:

(1) —C_1 –C_5 alkyl-Q^5,

(2) —O—C_1 –C_5 alkyl-Q^5,

(3) —S—C_1 –C_5 alkyl-Q^5,

(4) —C_1 –C_3 alkyl-O—C_1 –C_3 alkyl-Q^5,

(5) —C_1 –C_3 alkyl-S—C_1 –C_3 alkyl-Q^5,

(6) —C_1 –C_5 alkyl-O—Q^5,

(7) —C_1 –C_5 alkyl-S—Q^5,

wherein the substituent resides on the alkyl and the substituent is C_1 – C_3 alkyl, and

R^{129}, $R^{129'}$, R^{130}, R^{131} and R^{132} are each independently selected from the group consisting of:

(a) hydrogen,

(b) C_1 –C_6 alkyl;

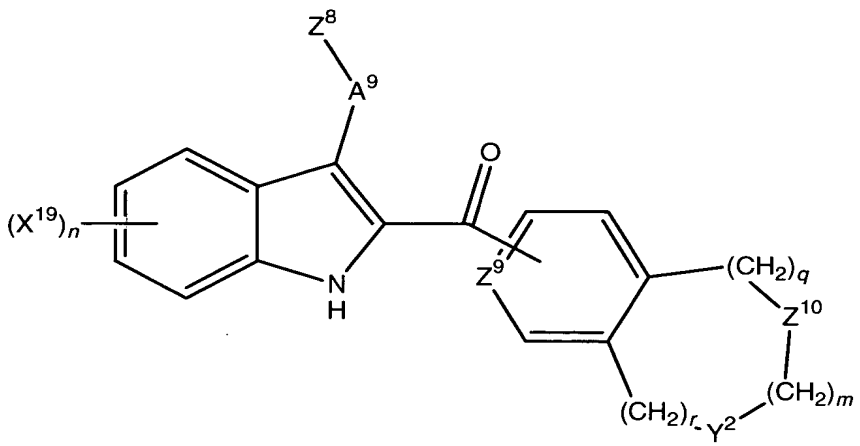
or R^{129} and R^{130} or R^{131} and R^{132} together with the carbon to which they are attached form a saturated monocyclic carbon ring of 3, 4, 5, 6 or 7 atoms;

Q^5 is CO_2H, CO_2—C_1–C_4 alkyl, tetrazolyl-5-yl, $C(R^{131})(R^{132})(OH)$, or $C(R^{131})(R^{132})(O$—C_1–C_4 alkyl);

provided that when X—Y—Z is —S—CR^{128}=$CR^{128'}$, then R^{128} and $R^{128'}$ are other than CF_3.

[000121] An exemplary phenyl heterocycle that is disclosed in U.S. Patent No. 6,239,173 is 3-phenyl-4-(4-(methylsulfonyl)phenyl)-2-(2H)-furanone.

[000122] Bicycliccarbonyl indole compounds such as those described in U.S. Patent No. 6,303,628 are useful as Cox-2 selective inhibitors of the present invention. Such bicycliccarbonyl indole compounds have the formula shown below in formula **XXV**:



XXV

or the pharmaceutically acceptable salts thereof wherein:

A^9 is C_1–C_6 alkylene or —NR^{133}—;

Z^8 is $C(=L^3)R^{134}$, or SO_2R^{135};

Z^9 is CH or N;

Z^{10} and Y^2 are independently selected from —CH_2—, O, S and —N—R^{133};

m is 1, 2 or 3;

q and r are independently 0, 1 or 2;

X^{18} is independently selected from halogen, C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkoxy, C_1 –C_4 alkylthio, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino and cyano;

n is 0, 1, 2, 3 or 4;

L^3 is oxygen or sulfur;

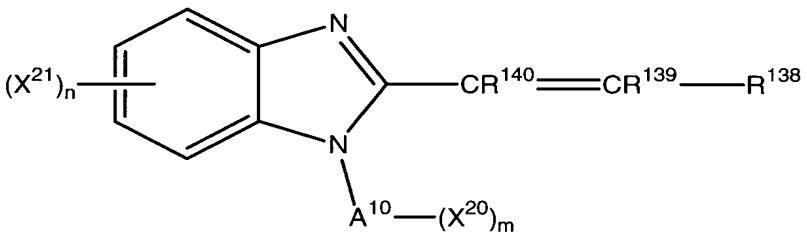
R^{133} is hydrogen or C_1 –C_4 alkyl;

R^{134} is hydroxyl, C_1 –C_6 alkyl, halo-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, halo-substituted C_1 –C_6 alkoxy, C_3 –C_7 cycloalkoxy, C_1 –C_4 alkyl(C_3 –C_7 cycloalkoxy), —NR^{136} R^{137}, C_1 –C_4 alkylphenyl-O— or phenyl-O—, said phenyl being optionally substituted with one to five substituents independently selected from halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy and nitro;

R^{135} is C_1 –C_6 alkyl or halo-substituted C_1 –C_6 alkyl; and

R^{136} and R^{137} are independently selected from hydrogen, $C_{1\text{-}6}$ alkyl and halo-substituted C_1 –C_6 alkyl.

[000123] Materials that can serve as a Cox-2 selective inhibitor of the present invention include benzimidazole compounds that are described in U.S. Patent No. 6,310,079. Such benzimidazole compounds have the formula shown below in formula **XXVI**:



XXVI

or a pharmaceutically acceptable salt thereof, wherein:

A^{10} is heteroaryl selected from

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom, or

a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and
said heteroaryl being connected to the nitrogen atom on the benzimidazole through a carbon atom on the heteroaryl ring;

X^{20} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amonio, N-(C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbamoyl, [N-(C_1 –C_4 alkyl)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

X^{21} is independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, hydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-(C_1 –C_4 alkyl)-N-(C_1 –C_4 alkanoyl) amino, N-[(C_1 –C_4 alkyl)sulfonyl]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)hydroxyl, cabamoyl, [N-(C_1 –C_4 alkyl) amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, N-carbomoylamino, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl;

R^{138} is selected from:

hydrogen;

straight or branched C_1 –C_4 alkyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from

halo, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_3 –C_8 cycloalkyl optionally substituted with one to three substituent(s) wherein said substituents are indepently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

C_4 –C_8 cycloalkenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halo-substituted C_1 –C_4 alkyl, □ydroxyl-substituted C_1 –C_4 alkyl, (C_1 –C_4 alkoxy)C_1 –C_4 alkyl, halo-substituted C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino, N, N-di(C_1 –C_4 alkyl)amino, [N-(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, [N, N-di(C_1 –C_4 alkyl)amino]C_1 –C_4 alkyl, N-(C_1 –C_4 alkanoyl)amino, N-[C_1 –C_4 alkyl)(C_1 –C_4 alkanoyl)]amino, N-[(C_1 –C_4 alkyl)sulfony]amino, N-[(halo-substituted C_1 –C_4 alkyl)sulfonyl]amino, C_1 –C_4 alkanoyl, carboxy, (C_1 –C_4 alkoxy)carbonyl, carbomoyl, [N-(C_1 –C_4 alky)amino]carbonyl, [N, N-di(C_1 –C_4 alkyl)amino]carbonyl, cyano, nitro, mercapto, (C_1 –C_4 alkyl)thio, (C_1 –C_4 alkyl)sulfinyl, (C_1 –C_4 alkyl)sulfonyl, aminosulfonyl, [N-(C_1 –C_4 alkyl)amino]sulfonyl and [N, N-di(C_1 –C_4 alkyl)amino]sulfonyl; and

heteroaryl selected from:

a 5-membered monocyclic aromatic ring having one hetero atom selected from O, S and N and optionally containing one to three N atom(s) in addition to said hetero atom; or a 6-membered monocyclic aromatic ring having one N atom and optionally containing one to four N atom(s) in addition to said N atom; and

said heteroaryl being optionally substituted with one to three substituent(s) selected from X^{20} ;

R^{139} and R^{140} are independently selected from:

hydrogen;

halo;

C_1 –C_4 alkyl;

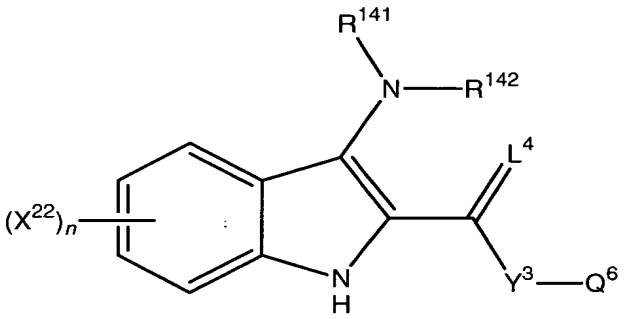
phenyl optionally substituted with one to three substituent(s) wherein said substituents are independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, amino, N-(C_1 –C_4 alkyl)amino and N, N-di(C_1 –C_4 alkyl)amino;

or R^{138} and R^{139} can form, together with the carbon atom to which they are attached, a C_3 –C_7 cycloalkyl ring;

m is 0, 1, 2, 3, 4 or 5; and

n is 0, 1, 2, 3 or 4.

[000124] Compounds that may be employed as a Cox-2 selective inhibitor of the present invention include indole compounds that are described in U.S. Patent No. 6,300,363. Such indole compounds have the formula shown below in formula **XXVII**:



XXVII

and the pharmaceutically acceptable salts thereof, wherein:

L^4 is oxygen or sulfur;

Y^3 is a direct bond or C_1 –C_4 alkylidene;

Q^6 is:

(a) C_1 –C_6 alkyl or halosubstituted C_1 –C_6 alkyl, said alkyl being optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkoxy, amino and mono- or di-(C_1 –C_4 alkyl)amino,

(b) C_3 –C_7 cycloalkyl optionally substituted with up to three substituents independently selected from hydroxyl, C_1 –C_4 alkyl and C_1 –C_4 alkoxy,

(c) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to four substituents independently selected from:

(c-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 $N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, $NHC(O)R^{143}$, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$ and —O—Y-phenyl, said phenyl being optionally substituted with one or two substituents independently selected from halo, C_1 –C_4 alkyl, CF_3, hydroxyl, OR^{143}, $S(O)_mR^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino and CN;

(d) a monocyclic aromatic group of 5 atoms, said aromatic group having one heteroatom selected from O, S and N and optionally containing up to three N atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substitutents independently selected from:

(d-1) halo, C_1 –C_4 alkyl, halosubstituted C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstituted C_1 –C_4 alkoxy, C_1 –C_4 alkyl-OH, $S(O)_m$ R^{143}, SO_2 NH_2, SO_2 $N(C_1$ –C_4 alkyl)$_2$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2$ R^{143}, $NHC(O)R^{143}$, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, phenyl, and mono-, di- or tri-substituted phenyl wherein the substituent is independently selected from halo, CF_3, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, OCF_3, SR^{143}, SO_2 CH_3, SO_2 NH_2, amino, $C_{1\text{-}4}$ alkylamino and $NHSO_2$ R^{143};

(e) a monocyclic aromatic group of 6 atoms, said aromatic group having one heteroatom which is N and optionally containing up to three atoms in addition to said heteroatom, and said aromatic group being substituted with up to three substituents independently selected from the above group (d-1);

R^{141} is hydrogen or C_1 –C_6 alkyl optionally substituted with a substituent selected independently from hydroxyl, OR^{143}, nitro, amino, mono- or di-(C_1

$-C_4$ alkyl)amino, CO_2H, CO_2 (C_1 $-C_4$ alkyl), $CONH_2$, $CONH(C_1$ $-C_4$ alkyl) and $CON(C_1$ $-C_4$ alkyl)$_2$;

R^{142} is:

(a) hydrogen,

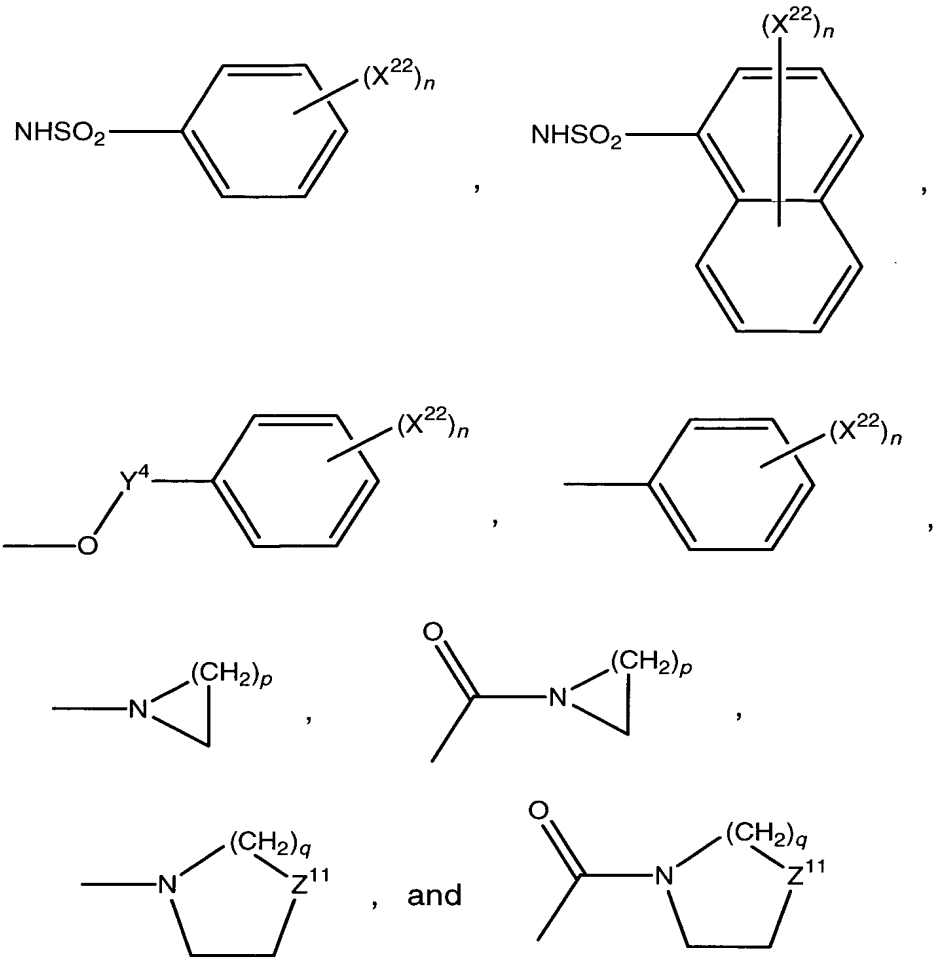
(b) C_1 $-C_4$ alkyl,

(c) $C(O)R^{145}$,

wherein R^{145} is selected from:

(c-1) C_1 $-C_{22}$ alkyl or C_2 $-C_{22}$ alkenyl, said alkyl or alkenyl being optionally substituted with up to four substituents independently selected from:

(c-1-1) halo, hydroxyl, OR^{143}, $S(O)_m$ R^{143}, nitro, amino, mono- or di-(C_1 $-C_4$ alkyl)amino, $NHSO_2$ R^{143}, CO_2H, CO_2 (C_1 $-C_4$ alkyl), $CONH_2$, $CONH(C_1$ $-C_4$ alkyl), $CON(C_1$ $-C_4$ alkyl)$_2$, $OC(O)R^{143}$, thienyl, naphthyl and groups of the following formulas:



(c-2) C_1 –C_{22} alkyl or C_2 –C_{22} alkenyl, said alkyl or alkenyl being optionally substituted with five to forty-five halogen atoms,

(c-3) –Y^5—C_3 –C_7 cycloalkyl or –Y^5—C_3 –C_7 cycloalkenyl, said cycloalkyl or cycloalkenyl being optionally substituted with up to three substituent independently selected from:

(c-3-1) C_1 –C_4 alkyl, hydroxyl, OR^{143}, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

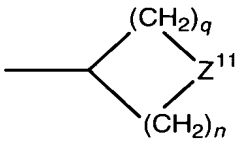
(c-4) phenyl or naphthyl, said phenyl or naphthyl being optionally substituted with up to seven (preferably up to seven) substituents independently selected from:

(c-4-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, halosubstituted C_1 –C_8 alkyl, halosubstituted C_1 –C_8 alkoxy, CN, nitro, $S(O)_m R^{143}$, $SO_2 NH_2$, $SO_2 NH(C_1$ –C_4 alkyl), $SO_2 N(C_1$ –C_4 alkyl)$_2$, amino, C_1 –C_4 alkylamino, di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, $OC(O)R^{143}$, and phenyl optionally substituted with up to three substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, OCH_3, CF_3, OCF_3, CN, nitro, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl) and $CONH_2$,

(c-5) a monocyclic aromatic group as defined in (d) and (e) above, said aromatic group being optionally substituted with up to three substituents independently selected from:

(c-5-1) halo, C_1 –C_8 alkyl, C_1 –C_4 alkyl-OH, hydroxyl, C_1 –C_8 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $CONH_2$, $CONH(C_1$ –C_4 alkyl), $CON(C_1$ –C_4 alkyl)$_2$, CO_2 H and CO_2 (C_1 –C_4 alkyl), and —Y-phenyl, said phenyl being optionally substituted with up to three substituents independently selected halogen, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, CF_3, OCF_3, CN, nitro, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, CO_2 H, CO_2 (C_1 –C_4 alkyl), $CONH_2$, $CONH(C_1$ –C_4 alkyl) and $CON(C_1$ –C_4 alkyl)$_2$,

(c-6) a group of the following formula:



X^{22} is halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, halosubstitutued C_1 –C_4 alkoxy, $S(O)_m R^{143}$, amino, mono- or di-(C_1 –C_4 alkyl)amino, $NHSO_2 R^{143}$, nitro, halosubstitutued C_1 –C_4 alkyl, CN, CO_2 H, CO_2 (C_1 –C_4 alkyl), C_1 –C_4 alkyl-OH, C_1 –C_4 alkylOR^{143}, $CONH_2$, $CONH(C_1$ –C_4 alkyl) or $CON(C_1$ –C_4 alkyl)$_2$;

R^{143} is C_1 –C_4 alkyl or halosubstituted C_1 –C_4 alkyl;

m is 0, 1 or 2; n is 0, 1, 2 or 3; p is 1, 2, 3, 4 or 5; q is 2 or 3;

Z^{11} is oxygen, sulfur or NR^{144} ; and

R^{144} is hydrogen, C_1 –C_6 alkyl, halosubstitutued C_1 –C_4 alkyl or –Y^5-phenyl, said phenyl being optionally substituted with up to two substituents independently selected from halo, C_1 –C_4 alkyl, hydroxyl, C_1 –C_4 alkoxy, $S(O)_m$ R^{143}, amino, mono- or di-(C_1 –C_4 alkyl)amino, CF_3, OCF_3, CN and nitro;

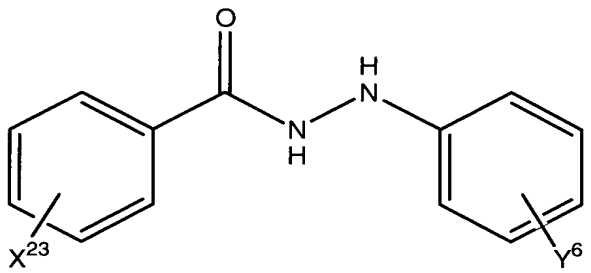
with the proviso that a group of formula –Y^5—Q is not methyl or ethyl when X^{22} is hydrogen;

L^4 is oxygen;

R^{141} is hydrogen; and

R^{142} is acetyl.

[000125] Aryl phenylhydrazides that are described in U.S. Patent No. 6,077,869 can serve as Cox-2 selective inhibitors of the present invention. Such aryl phenylhydrazides have the formula shown below in formula **XXVIII**:



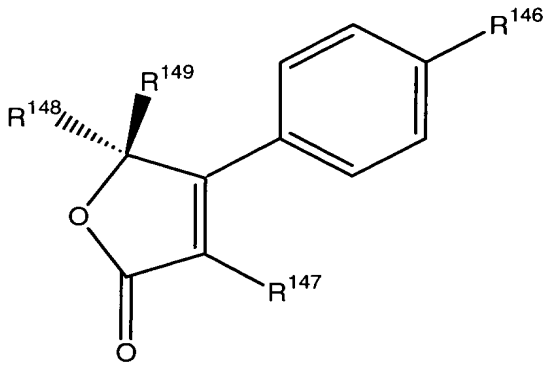
XXVIII

wherein:

X^{23} and Y^6 are selected from hydrogen, halogen, alkyl, nitro, amino, hydroxy, methoxy and methylsulfonyl;

or a pharmaceutically acceptable salt thereof,.

[000126] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-aryloxy, 4-aryl furan-2-ones that are described in U.S. Patent No. 6,140,515. Such 2-aryloxy, 4-aryl furan-2-ones have the formula shown below in formula **XXIX**:



XXIX

or a pharmaceutical salt thereof, wherein:

R^{146} is selected from the group consisting of SCH_3, $—S(O)_2 CH_3$ and $—S(O)_2 NH_2$;

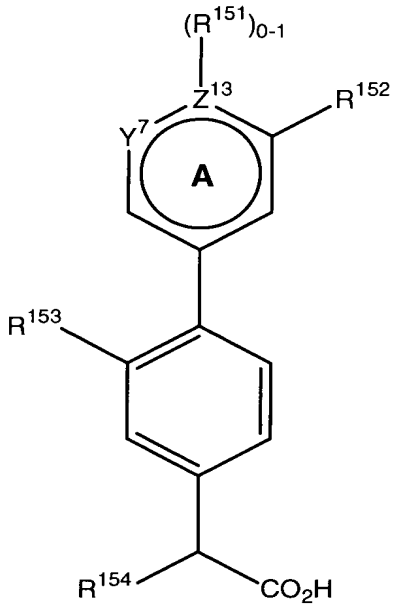
R^{147} is selected from the group consisting of OR^{150}, mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{150} is unsubstituted or mono or di-substituted phenyl or pyridyl wherein the substituents are selected from the group consisting of methyl, chloro and F;

R^{148} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br; and

R^{149} is H, C_1 –C_4 alkyl optionally substituted with 1 to 3 groups of F, Cl or Br, with the proviso that R^{148} and R^{149} are not the same.

[000127] Materials that can serve as a Cox-2 selective inhibitor of the present invention include bisaryl compounds that are described in U.S. Patent No. 5,994,379. Such bisaryl compounds have the formula shown below in formula **XXX**:



XXX

or a pharmaceutically acceptable salt, ester or tautomer thereof, wherein:

Z^{13} is C or N;

when Z^{13} is N, R^{151} represents H or is absent, or is taken in conjunction with R^{152} as described below:

when Z^{13} is C, R^{151} represents H and R^{152} is a moiety which has the following characteristics:

(a) it is a linear chain of 3-4 atoms containing 0-2 double bonds, which can adopt an energetically stable transoid configuration and if a double bond is present, the bond is in the trans configuration,

(b) it is lipophilic except for the atom bonded directly to ring A, which is either lipophilic or non-lipophilic, and

(c) there exists an energetically stable configuration planar with ring A to within about 15 degrees;

or R^{151} and R^{152} are taken in combination and represent a 5- or 6-membered aromatic or non-aromatic ring D fused to ring A, said ring D containing 0-3 heteroatoms selected from O, S and N;

said ring D being lipophilic except for the atoms attached directly to ring A, which are lipophilic or non-lipophilic, and said ring D having available an

energetically stable configuration planar with ring A to within about 15 degrees;

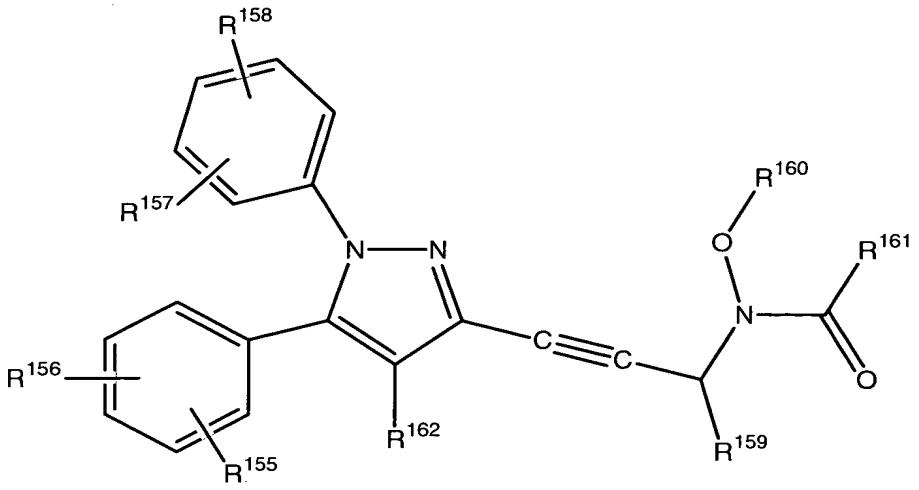
said ring D further being substituted with 1 R^a group selected from the group consisting of: C_1 –C_2 alkyl, —OC_1 –C_2 alkyl, —NHC_1 –C_2 alkyl, —$N(C_1$ –C_2 alkyl$)_2$, —C(O) C_1 –C_2 alkyl, —S—C_1 –C_2 alkyl and —C(S) C_1 –C_2 alkyl;

Y^7 represents N, CH or C—OC_1 –C_3 alkyl, and when Z^{13} is N, Y^7 can also represent a carbonyl group;

R^{153} represents H, Br, Cl or F; and

R^{154} represents H or CH_3.

[000128] Compounds useful as Cox-2 selective inhibitors of the present invention include 1,5-diarylpyrazoles that are described in U.S. Patent No. 6,028,202. Such 1,5-diarylpyrazoles have the formula shown below in formula **XXXI**:



XXXI

wherein:

R^{155}, R^{156}, R^{157}, and R^{158} are independently selected from the groups consisting of hydrogen, C_1 –C_5 alkyl, C_1 –C_5 alkoxy, phenyl, halo, hydroxyl, C_1 –C_5 alkylsulfonyl, C_1 –C_5 alkylthio, trihaloC_1 –C_5 alkyl, amino, nitro and 2-quinolinylmethoxy;

R^{159} is hydrogen, C_1 –C_5 alkyl, trihaloC_1 –C_5 alkyl, phenyl, substituted phenyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro or R^{159} is heteroaryl of 5-7 ring members where at least one of the ring members is nitrogen, sulfur or oxygen;

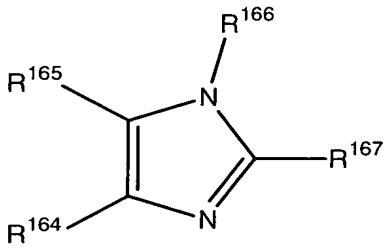
R^{160} is hydrogen, C_1 –C_5 alkyl, phenyl C_1 –C_5 alkyl, substituted phenyl C_1 –C_5 alkyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro, or R^{160} is C_1 –C_5 alkoxycarbonyl, phenoxycarbonyl, substituted phenoxycarbonyl where the phenyl substitutents are halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro;

R^{161} is C_1 –C_{10} alkyl, substituted C_1 –C_{10} alkyl where the substituents are halogen, trihaloC_1 –C_5 alkyl, C_1 –C_5 alkoxy, carboxy, C_1 –C_5 alkoxycarbonyl, amino, C_1 –C_5 alkylamino, diC_1 –C_5 alkylamino, diC_1 –C_5 alkylaminoC_1 –C_5 alkylamino, C_1 –C_5 alkylaminoC_1 –C_5 alkylamino or a heterocycle containing 4-8 ring atoms where one more of the ring atoms is nitrogen, oxygen or sulfur, where said heterocycle may be optionally substituted with C_1 –C_5 alkyl; or R^{161} is phenyl, substituted phenyl (where the phenyl substitutents are one or more of C_1 –C_5 alkyl, halogen, C_1 –C_5 alkoxy, trihaloC_1 –C_5 alkyl or nitro), or R^{161} is heteroaryl having 5-7 ring atoms where one or more atoms are nitrogen, oxygen or sulfur, fused heteroaryl where one or more 5-7 membered aromatic rings are fused to the heteroaryl; or

R^{161} is NR^{163} R^{164} where R^{163} and R^{164} are independently selected from hydrogen and $C_{1\text{-}5}$ alkyl or R^{163} and R^{164} may be taken together with the depicted nitrogen to form a heteroaryl ring of 5-7 ring members where one or more of the ring members is nitrogen, sulfur or oxygen where said heteroaryl ring may be optionally substituted with C_1 –C_5 alkyl; R^{162} is hydrogen, C_1 –C_5 alkyl, nitro, amino, and halogen;

and pharmaceutically acceptable salts thereof.

[000129] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 2-substituted imidazoles that are described in U.S. Patent No. 6,040,320. Such 2-substituted imidazoles have the formula shown below in formula **XXXII**:



XXXII

wherein:

R^{164} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms, or

substituted phenyl;

wherein the substituents are independently selected from one or members of the group consisting of C_{1-5} alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{165} is phenyl, heteroaryl wherein the heteroaryl contains 5 to 6 ring atoms,

substituted heteroaryl;

wherein the substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl and halogen, or

substituted phenyl,

wherein the substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen, nitro, trifluoromethyl and nitrile;

R^{166} is hydrogen, 2-(trimethylsilyl)ethoxymethyl), C_1 –C_5 alkoxycarbonyl, aryloxycarbonyl, arylC_1 –C_5 alkyloxycarbonyl, arylC_1 –C_5 alkyl, phthalimidoC_1 –C_5 alkyl, aminoC_1 –C_5 alkyl, diaminoC_1 –C_5 alkyl, succinimidoC_1 –C_5 alkyl, C_1 –C_5 alkylcarbonyl, arylcarbonyl, C_1 –C_5 alkylcarbonylC_1 –C_5 alkyl, aryloxycarbonylC_1 –C_5 alkyl, heteroarylC_1 –C_5 alkyl where the heteroaryl contains 5 to 6 ring atoms, or

substituted arylC_1 –C_5 alkyl,

wherein the aryl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, C_1 –C_5 alkoxy, halogen, amino, C_1 –C_5 alkylamino, and diC_1 –C_5 alkylamino;

R^{167} is $(A^{11})_n$ –$(CH^{165})_q$ –X^{24} wherein:

A^{11} is sulfur or carbonyl;

n is 0 or 1;

q is 0-9;

X^{24} is selected from the group consisting of hydrogen, hydroxyl, halogen, vinyl, ethynyl, C_1 –C_5 alkyl, C_3 –C_7 cycloalkyl, C_1 –C_5 alkoxy, phenoxy, phenyl, arylC_1 –C_5 alkyl, amino, C_1 –C_5 alkylamino, nitrile, phthalimido, amido, phenylcarbonyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylthio, C_1 –C_5 alkylsulfonyl, phenylsulfonyl,

substituted sulfonamido,

wherein the sulfonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, araC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl;

substituted vinyl,

wherein the substituents are independently selected from one or members of the group consisting of fluorine, bromine, chlorine and iodine,

substituted ethynyl,

wherein the substituents are independently selected from one or more members of the group consisting of fluorine, bromine chlorine and iodine,

substituted C_1 –C_5 alkyl,

wherein the substituents are selected from the group consisting of one or more C_1 –C_5 alkoxy, trihaloalkyl, phthalimido and amino,

substituted phenyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted phenoxy,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkoxy,

wherein the alkyl substituent is selected from the group consisting of phthalimido and amino,

substituted arylC_1 –C_5 alkyl,

wherein the alkyl substituent is hydroxyl,

substituted arylC_1 –C_5 alkyl,

wherein the phenyl substituents are independently selected from one or more members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted amido,

wherein the carbonyl substituent is selected from the group consisting of C_1 –C_5 alkyl, phenyl, arylC_1 –C_5 alkyl, thienyl, furanyl, and naphthyl,

substituted phenylcarbonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of C_1 –C_5 alkyl, halogen and C_1 –C_5 alkoxy,

substituted C_1 –C_5 alkylthio,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted C_1 –C_5 alkylsulfonyl,

wherein the alkyl substituent is selected from the group consisting of hydroxyl and phthalimido,

substituted phenylsulfonyl,

wherein the phenyl substituents are independently selected from one or members of the group consisting of bromine, fluorine, chlorine, C_1 –C_5 alkoxy and trifluoromethyl,

with the proviso:

if A^{11} is sulfur and X^{24} is other than hydrogen, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl, then q must be equal to or greater than 1;

if A^{11} is sulfur and q is 1, then X^{24} cannot be C_1 –C_2 alkyl;

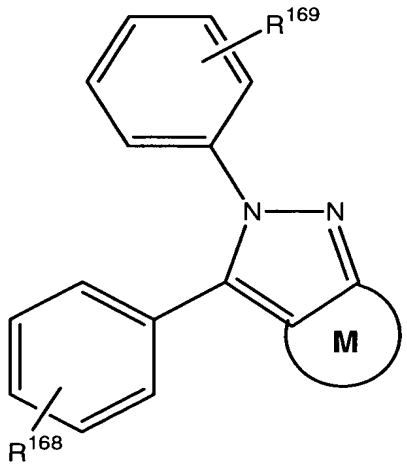
if A^{11} is carbonyl and q is 0, then X^{24} cannot be vinyl, ethynyl, C_1 –C_5 alkylaminocarbonyl, phenylaminocarbonyl, arylC_1 –C_5 alkylaminocarbonyl, C_1 –C_5 alkylsulfonyl or phenylsulfonyl;

if A^{11} is carbonyl, q is 0 and X^{24} is H, then R^{166} is not 2-(trimethylsilyl)ethoxymethyl;

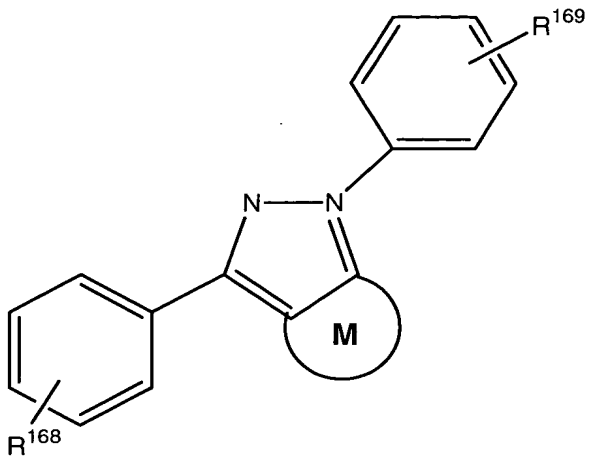
if n is 0 and q is 0, then X^{24} cannot be hydrogen;

and pharmaceutically acceptable salts thereof.

[000130] Materials that can serve as a Cox-2 selective inhibitor of the present invention include 1,3- and 2,3-diarylcycloalkano and cycloalkeno pyrazoles that are described in U.S. Patent No. 6,083,969. Such 1,3- and 2,3-diarylpyrazole compounds have the general formulas shown below in formulas **XXXIII** and **XXXIV**:



XXXIII

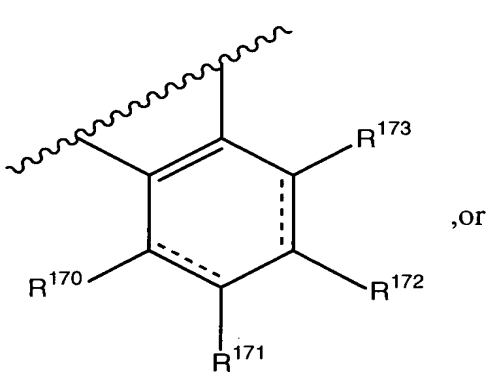


XXXIV

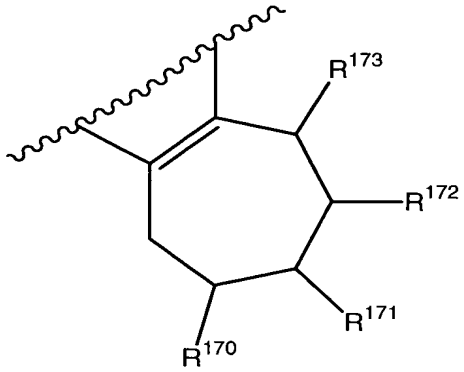
wherein:

R^{168} and R^{169} are independently selected from the group consisting of hydrogen, halogen, $(C_1 –C_6)$alkyl, $(C_1 –C_6)$alkoxy, nitro, amino, □ydroxyl, trifluoro, —S$(C_1 –C_6)$alkyl, —SO$(C_1 –C_6)$alkyl and —SO_2 $(C_1 –C_6)$alkyl; and

the fused moiety M is a group selected from the group consisting of an optionally substituted cyclohexyl and cycloheptyl group having the formulae:



,or



wherein:

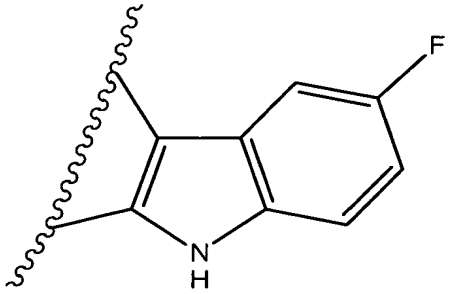
R^{170} is selected from the group consisting of hydrogen, halogen, hydroxyl and carbonyl;

or R^{170} and R^{171} taken together form a moiety selected from the group consisting of —$OCOCH_2$ —, —$ONH(CH_3)COCH_2$ —, —OCOCH= and —O—;

R^{171} and R^{172} are independently selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy, =NOH, —NR^{174} R^{175}, —OCH_3, —OCH_2 CH_3, —OSO_2 $NHCO_2$ CH_3, =$CHCO_2$ CH_2 CH_3, —CH_2 CO_2 H, —CH_2 CO_2 CH_3, —CH_2 CO_2 CH_2 CH_3, —CH_2 $CON(CH_3)_2$, —CH_2 CO_2 $NHCH_3$, —$CHCHCO_2$ CH_2 CH_3, —$OCON(CH_3)OH$, —$C(COCH_3)_2$, di(C_1 –C_6)alkyl and di(C_1 –C_6)alkoxy;

R^{173} is selected from the group consisting of hydrogen, halogen, hydroxyl, carbonyl, amino, (C_1 –C_6)alkyl, (C_1 –C_6)alkoxy and optionally substituted carboxyphenyl, wherein substituents on the carboxyphenyl group are selected from the group consisting of halogen, hydroxyl, amino, (C_1 –C_6)alkyl and (C_1 –C_6)alkoxy;

or R^{172} and R^{173} taken together form a moiety selected from the group consisting of —O—and



R^{174} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$ and (C_1 –C_6)alkyl; and

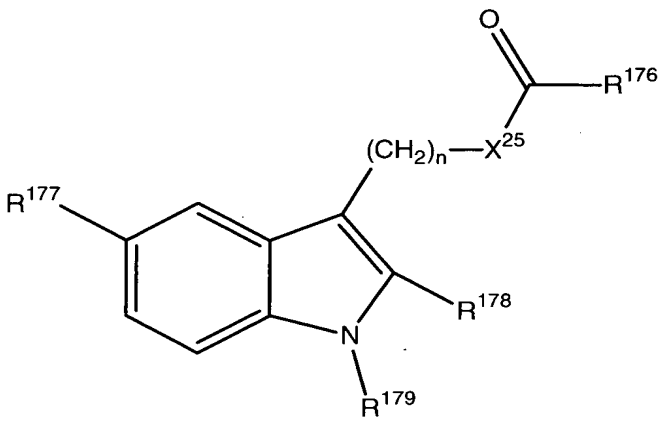
R^{175} is selected from the group consisting of hydrogen, OH, —$OCOCH_3$, —$COCH_3$, (C_1 –C_6)alkyl, —$CONH_2$ and —SO_2 CH_3 ;

with the proviso that

if M is a cyclohexyl group, then R^{170} through R^{173} may not all be hydrogen; and

pharmaceutically acceptable salts, esters and pro-drug forms thereof.

[000131] Esters derived from indolealkanols and novel amides derived from indolealkylamides that are described in U.S. Patent No. 6,306,890 can serve as Cox-2 selective inhibitors of the present invention. Such compounds have the general formula shown below in formula **XXXV**:



XXXV

wherein:

R^{176} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_1 –C_6 hydroxyalkyl, branched C_1 –C_6 hydroxyalkyl, hydroxyl substituted C_4 –C_8 aryl, primary, secondary or tertiary C_1 –C_6 alkylamino, primary, secondary or tertiary branched C_1 –C_6 alkylamino, primary, secondary or tertiary C_4 –C_8 arylamino, C_1 –C_6 alkylcarboxylic acid, branched C_1 –C_6 alkylcarboxylic acid, C_1 –C_6 alkylester, branched C_1 –C_6 alkylester, C_4 –C_8 aryl, C_4 –C_8 arylcarboxylic acid, C_4 –C_8 arylester, C_4 –C_8 aryl substituted C_1 –C_6 alkyl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, or halo-substituted versions thereof, where halo is chloro, bromo, fluoro or iodo;

R^{177} is C_1 –C_6 alkyl, C_1 –C_6 branched alkyl, C_4 –C_8 cycloalkyl, C_4 –C_8 aryl, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, C_1 –C_6 alkoxy, C_1 –C_6 branched alkoxy, C_4 –C_8 aryloxy, or halo-substituted versions thereof or R^{177} is halo where halo is chloro, fluoro, bromo, or iodo;

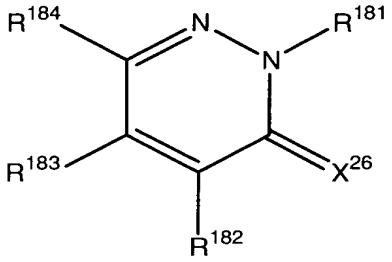
R^{178} is hydrogen, C_1 –C_6 alkyl or C_1 –C_6 branched alkyl;

R^{179} is C_1 –C_6 alkyl, C_4 –C_8 aroyl, C_4 –C_8 aryl, C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, C_4 –C_8 aryl-substituted C_1 –C_6 alkyl, alkyl-substituted or aryl-substituted C_4 –C_8 heterocyclic alkyl or aryl with O, N or S in the ring, alkyl-substituted C_4 –C_8 aroyl, or alkyl-substituted C_4 –C_8 aryl, or halo-substituted versions thereof where halo is chloro, bromo, or iodo;

n is 1, 2, 3, or 4; and

X^{25} is O, NH, or N—R^{180}, where R^{180} is C_1 –C_6 or C_1 –C_6 branched alkyl.

[000132] Materials that can serve as a Cox-2 selective inhibitor of the present invention include pyridazinone compounds that are described in U.S. Patent No. 6,307,047. Such pyridazinone compounds have the formula shown below in formula **XXXVI**:



XXXVI

or a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein:

X^{26} is selected from the group consisting of O, S, —NR^{185}, —NOR^a, and –$NNR^b R^c$;

R^{185} is selected from the group consisting of alkenyl, alkyl, aryl, arylalkyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, heterocyclic, and heterocyclic alkyl;

R^a, R^b, and R^c are independently selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl, and cycloalkylalkyl;

R^{181} is selected from the group consisting of alkenyl, alkoxy, alkoxyalkyl, alkoxyiminoalkoxy, alkyl, alkylcarbonylalkyl, alkylsulfonylalkyl, alkynyl, aryl, arylalkenyl, arylalkoxy, arylalkyl, arylalkynyl, arylhaloalkyl, arylhydroxyalkyl, aryloxy, aryloxyhaloalkyl, aryloxyhydroxyalkyl, arylcarbonylalkyl, carboxyalkyl, cyanoalkyl, cycloalkenyl, cycloalkenylalkyl,

cycloalkyl, cycloalkylalkyl, cycloalkylidenealkyl, haloalkenyl, haloalkoxyhydroxyalkyl, haloalkyl, haloalkynyl, heterocyclic, heterocyclic alkoxy, heterocyclic alkyl, heterocyclic oxy, hydroxyalkyl, hydroxyiminoalkoxy, $—(CH_2)_n C(O)R^{186}$, $—(CH_2)_n CH(OH)R^{186}$, $—(CH_2)_n C(NOR^d)R^{186}$, $—(CH_2)_n CH(NOR^d)R^{186}$, $—(CH_2)_n CH(NR^d R^e)R^{186}$, $—R^{187} R^{188}$, $—(CH_2)_n C\equiv CR^{188}$, $—(CH_2)_n [CH(CX^{26'}_3)]_m (CH_2)_p R^{188}$, $—(CH_2)_n (CX^{26'}_2)_m (CH_2)_p R^{188}$, and $—(CH_2)_n (CHX^{26'})_m (CH_2)_m R^{188}$;

R^{186} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkenyl, haloalkyl, haloalkynyl, heterocyclic, and heterocyclic alkyl;

R^{187} is selected from the group consisting of alkenylene, alkylene, halo-substituted alkenylene, and halo-substituted alkylene;

R^{188} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkyl, cycloalkenyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

R^d and R^e are independently selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl, aryl, arylalkyl, cycloalkenyl, cycloalkyl, haloalkyl, heterocyclic, and heterocyclic alkyl;

$X^{26'}$ is halogen;

m is an integer from 0-5;

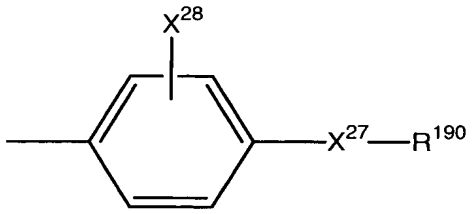
n is an integer from 0-10;

p is an integer from 0-10;

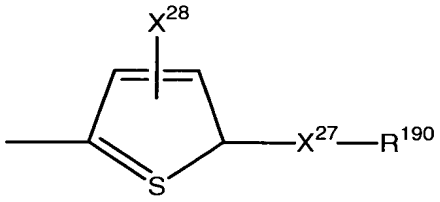
R^{182}, R^{183}, and R^{184} are independently selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkoxyiminoalkoxy, alkoxyiminoalkyl, alkyl, alkynyl, alkylcarbonylalkoxy, alkylcarbonylamino, alkylcarbonylaminoalkyl, aminoalkoxy, aminoalkylcarbonyloxyalkoxy aminocarbonylalkyl, aryl, arylalkenyl, arylalkyl, arylalkynyl, carboxyalkylcarbonyloxyalkoxy, cyano, cycloalkenyl, cycloalkyl, cycloalkylidenealkyl, haloalkenyloxy, haloalkoxy, haloalkyl, halogen, heterocyclic, hydroxyalkoxy, hydroxyiminoalkoxy, hydroxyiminoalkyl, mercaptoalkoxy, nitro, phosphonatoalkoxy, Y^8, and Z^{14};

provided that one of R^{182}, R^{183}, or R^{184} must be Z^{14}, and further provided that only one of R^{182}, R^{183}, or R^{184} is Z^{14};

Z^{14} is selected from the group consisting of:



and



X^{27} is selected from the group consisting of $S(O)_2$, $S(O)(NR^{191})$, $S(O)$, $Se(O)_2$, $P(O)(OR^{192})$, and $P(O)(NR^{193}\ R^{194})$;

X^{28} is selected from the group consisting of hydrogen, alkenyl, alkyl, alkynyl and halogen;

R^{190} is selected from the group consisting of alkenyl, alkoxy, alkyl, alkylamino, alkylcarbonylamino, alkynyl, amino, cycloalkenyl, cycloalkyl, dialkylamino, —$NHNH_2$, and —$NCHN(R^{191})R^{192}$;

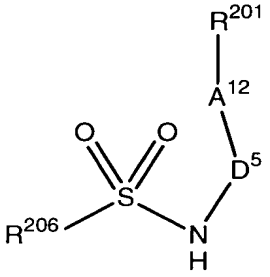
R^{191}, R^{192}, R^{193}, and R^{194} are independently selected from the group consisting of hydrogen, alkyl, and cycloalkyl, or R^{193} and R^{194} can be taken together, with the nitrogen to which they are attached, to form a 3-6 membered ring containing 1 or 2 heteroatoms selected from the group consisting of O, S, and NR^{188} ;

Y^8 is selected from the group consisting of –OR^{195}, —SR^{195}, —$C(R^{197})(R^{198})R^{195}$, —$C(O)R^{195}$, —$C(O)OR^{195}$, —$N(R^{197})C(O)R^{195}$, —$NC(R^{197})R^{195}$, and —$N(R^{197})R^{195}$;

R^{195} is selected from the group consisting of hydrogen, alkenyl, alkoxyalkyl, alkyl, alkylthioalkyl, alkynyl, cycloalkenyl, cycloalkenylalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, heterocyclic alkyl, hydroxyalkyl, and $NR^{199}\ R^{200}$; and

R^{197}, R^{198}, R^{199}, and R^{200} are independently selected from the group consisting of hydrogen, alkenyl, alkoxy, alkyl, cycloalkenyl, cycloalkyl, aryl, arylalkyl, heterocyclic, and heterocyclic alkyl.

[000133] Benzosulphonamide derivatives that are described in U.S. Patent No. 6,004,948 are useful as Cox-2 selective inhibitors of the present invention. Such benzosulphonamide derivatives have the formula shown below in formula **XXXVII**:



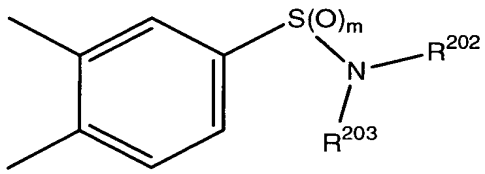
XXXVII

wherein:

A^{12} denotes oxygen, sulphur or NH;

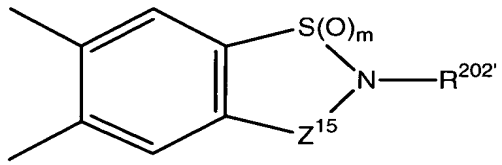
R^{201} denotes a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted by halogen, alkyl, CF_3 or alkoxy;

D^5 denotes a group of formula **XXXVIII** or **XXXIX**:



XXXVIII

or



XXXIX

R^{202} and R^{203} independently of each other denote hydrogen, an optionally polyfluorinated alkyl radical, an aralkyl, aryl or heteroaryl radical or a radical $(CH_2)_n -X^{29}$; or

R^{202} and R^{203} together with the N-atom denote a three- to seven-membered, saturated, partially or totally unsaturated heterocycle with one

or more heteroatoms N, O, or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $(CH_2)_n -X^{29}$, $R^{202,}$ denotes hydrogen, an optionally polyfluorinated alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n -X^{29}$,

wherein:

X^{29} denotes halogen, NO_2, —OR^{204}, —COR^{204}, —$CO_2 R^{204}$, —$OCO_2 R^{204}$, —CN, —$CONR^{204} OR^{205}$, —$CONR^{204} R^{205}$, —SR^{204}, —$S(O)R^{204}$, —$S(O)_2 R^{204}$, —$NR^{204} R^{205}$, —$NHC(O)R^{204}$, —$NHS(O)_2 R^{204}$;

Z^{15} denotes $-CH_2$ —, —CH_2 $-CH_2$ —, —CH_2 $-CH_2$ $-CH_2$ —, —CH_2 –CH=CH—, —CH=CH—CH_2 —, —CH_2 —CO—, —CO—CH_2 —, —NHCO—, —CONH—, —$NHCH_2$ —, —CH_2 NH—, —N=CH—, —NHCH—, —CH_2–CH_2—NH—, —CH=CH—, >N—R^{203}, >C=O, $>S(O)_m$;

R^{204} and R^{205} independently of each other denote hydrogen, alkyl, aralkyl or aryl;

n is an integer from 0 to 6;

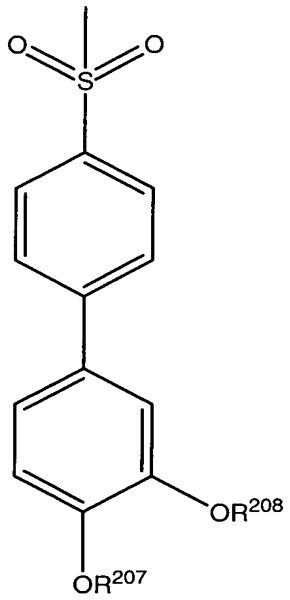
R^{206} is a straight-chained or branched C_1 –C_4 alkyl group which may optionally be mono- or polysubstituted by halogen or alkoxy, or R^{206} denotes CF_3; and

m denotes an integer from 0 to 2;

with the proviso that A^{12} does not represent O if R^{206} denotes CF_3;

and the pharmaceutically acceptable salts thereof.

[000134] Materials that can serve as Cox-2 selective inhibitors of the present invention include methanesulfonyl-biphenyl derivatives that are described in U.S. Patent No. 6,583,321. Such methanesulfonyl-biphenyl derivatives have the formula shown below in formula **XXXX**:



XXXX

wherein:

R^{207} and R^{208} are respectively a hydrogen;

C_1 –C_4-alkyl substituted or not substituted by halogens;

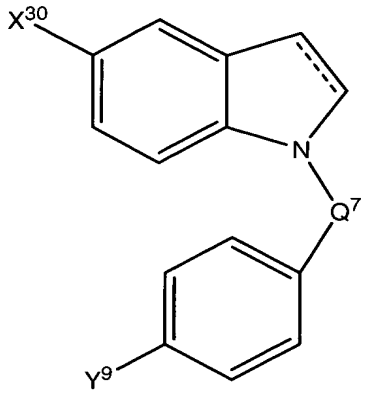
C_3 –C_7-cycloalkyl;

C_1 –C_5-alkyl containing 1-3 ether bonds and/or an aryl substitute;

substituted or not substituted phenyl;

or substituted or not substituted five or six ring-cycled heteroaryl containing more than one hetero atoms selected from a group consisting of nitrogen, sulfur, and oxygen (wherein phenyl or heteroaryl can be one- or multi-substituted by a substituent selected from a group consisting of hydrogen, methyl, ethyl, and isopropyl).

[000135] Cox-2 selective inhibitors such as 1H-indole derivatives described in U.S. Patent No. 6,599,929 are useful in the present invention. Such 1H-indole derivatives have the formula shown below in formula **XXXXI**:



XXXXI

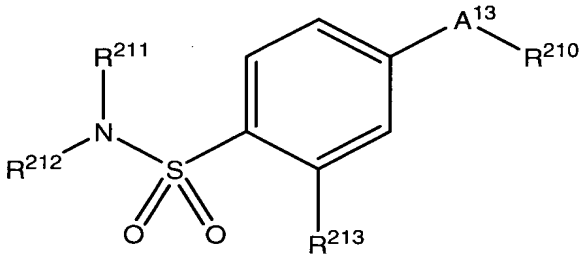
wherein:

X^{30} is $-NHSO_2R^{209}$ wherein R^{209} represents hydrogen or C_1 $-C_3$–alkyl;

Y^9 is hydrogen, halogen, C_1 $-C_3$–alkyl substituted or not substituted by halogen, NO_2, NH_2, OH, OMe, CO_2H, or CN; and

Q^7 is C=O, C=S, or CH_2.

[000136] Compounds that are useful as Cox-2 selective inhibitors of the present invention include prodrugs of Cox-2 inhibitors that are described in U.S. Patent Nos. 6,436,967 and 6,613,790. Such prodrugs of Cox-2 inhibitors have the formula shown below in formula **XXXXII**:



XXXXII

wherein:

A^{13} is a ring substituent selected from partially unsaturated heterocyclic, heteroaryl, cycloalkenyl and aryl, wherein A^{13} is unsubstituted or substituted with one or more radicals selected from alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, nitro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulfonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, cycloalkylalkyl, alkenyl, alkynyl, heterocycloxy, alkylthio, cycloalkyl, aryl,

heterocyclyl, cycloalkenyl, aralkyl, heterocyclylalkyl, alkylthioalkyl, arylcarbonyl, aralkylcarbonyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, araalkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, N-arylaminocarbonyl, N-alkyl-N-arylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, -arylamino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-arylamino, aminoalkyl, alkylaminoalkyl, N-arylaminoalkyl, N-aralkylaminoalkyl, N-alkyl-N-arylaminoalkyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfinyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl;

R^{210} is selected from heterocyclyl, cycloalkyl, cycloalkenyl, and aryl, wherein R^{210} is unsubstituted or substituted with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} is selected from hydrido and alkoxycarbonylalkyl;

R^{212} is selected from alkyl, carboxyalkyl, acyl, alkoxycarbonyl, heteroarylcarbonyl, alkoxycarbonylalkylcarbonyl, alkoxycarbonylcarbonyl, amino acid residue, and alkylcarbonylaminoalkylcarbonyl;

provided A^{13} is not tetrazolium, or pyridinium; and further provided A^{13} is not indanone when R^{212} is alkyl or carboxyalkyl; further provided A^{13} is not thienyl, when R^{210} is 4-fluorophenyl, when R^{211} is hydrido, and when R^{212} is methyl or acyl; and

R^{213} is hydrido;

or a pharmaceutically-acceptable salt thereof.

[000137] Specific non-limiting examples of substituted sulfonamide prodrugs of Cox-2 inhibitors disclosed in U.S. Patent No. 6,436,967 that are useful in the present invention include:

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]propanamide;

N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phen yl]sulfonyl]butanamide;

N-[[4-[1,5-dimethyl)-3-phenyl-1H-pyrazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-(3-pyridinyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]butanamide;
N-[[4-[2-(3-chloro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(3-fluorophenyl)-5-methylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
2-methyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]benzamide;
2,2-dimethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
N-[[4-5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]pentanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]hexanamide;
3-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]propanamide;
2-ethoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-methyl-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H pyrazol-1-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]butanamide;

N-[[4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-6-fluoro-1,5-dihydro-7-methoxy-[2]benzothiopyrano [4,3-c]pyrazol-1-yl)phenyl]sulfonyl]acetamide;
N-[[4-[6-fluoro-1,5-dihydro-7-methoxy-3-(trifluoromethyl)-[2]benzothiopyrano[4,3-c]pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]phenyl]sulfonyl]acetamide;
N-[[4-(2-methyl-4-phenyloxazol-5-yl)phenyl]sulfonyl]acetamide;
methyl[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]oxoacetate;
2-methoxy-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]propanamide;
N-[[4-[5-(difluoromethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]butanamide;
N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]formamide;
1,1-dimethylethyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-[[.sup.4 -(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine;
2-amino-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
2-(acetylamino)-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]acetamide;
methyl 4-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-4-oxobutanoate;
methyl N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]carbamate;
N-acetyl-N-[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]glycine, ethyl ester;
N-[[4-(5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)phenyl]sulfonyl]acetamide;
methyl 3-[[[4-(5-methyl-3-phenylisoxazol-4-yl)phenyl]sulfonyl]amino]-3-oxopropanoate;

4-[5-(3-bromo-5-fluoro-4-methoxyphenyl)-2-(trifluoromethyl)oxazol-4-yl]-N-methylbenezenesulfonamide;
N-(1,1-dimethylethyl)-4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide;
4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-N-methylbenzenesulfonamide;
N-methyl-4-(5-methyl-3-phenylisoxazol-4-yl)benezenesulfonamide;
N-[[4-[5-(hydroxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide:
N-[[4-[5-(acetoxymethyl)-3-phenylisoxazol-4-yl]phenyl]sulfonyl]acetamide;
N-[[4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl)phenyl]sulfonyl]acetamide;
4-[2-(4-fluorophenyl)-1H-pyrrol-1-yl]-N-methylbenzenesulfonamide;
N-[[4-(3,4-dimethyl-1-phenyl-1H-pyrazol-5-yl]phenyl]sulfonyl]propanamide;
N-[[4-[2-(2-methylpyridin-3-yl)-4-trifluoromethylimidazol-1-yl]phenyl]sulfonyl]propanamide;
4-[2-(4-fluorophenyl)cyclopenten-1-yl]-N-methylbenezenesulfonamide; and
N-[[4-(3-phenyl-2,3-dihydro-2-oxofuran-4-yl)phenyl]sulfonyl]propanamide.

[000138] Those prodrugs disclosed in U.S. Patent No. 6,613,790 have the general formula shown above in formula **XXXXII** wherein:

A^{13} is a pyrazole group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkylcarbonyl, formyl, halo, alkyl, haloalkyl, oxo, cyano, intro, carboxyl, alkoxy, aminocarbonyl, alkoxycarbonyl, carboxyalkyl, cyanoalkyl, hydroxyalkyl, haloalkylsulonyloxy, alkoxyalkyloxyalkyl, carboxyalkoxyalkyl, alkenyl, alkynyl, alkylthio, alkylthioalkyl, alkoxyalkyl, alkoxycarbonylalkyl, aminocarbonylalkyl, alkylaminocarbonyl, alkylaminocarbonylalkyl, alkylamino, aminoalkyl, alkylaminoalkyl, alkylsutfinyl, alkylsulfonyl, aminosulfonyl, and alkylaminosulfonyl;

R^{210} is a phenyl group optionally substituted at a substitutable position with one or more radicals independently selected at each occurrence from the group consisting of alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl,

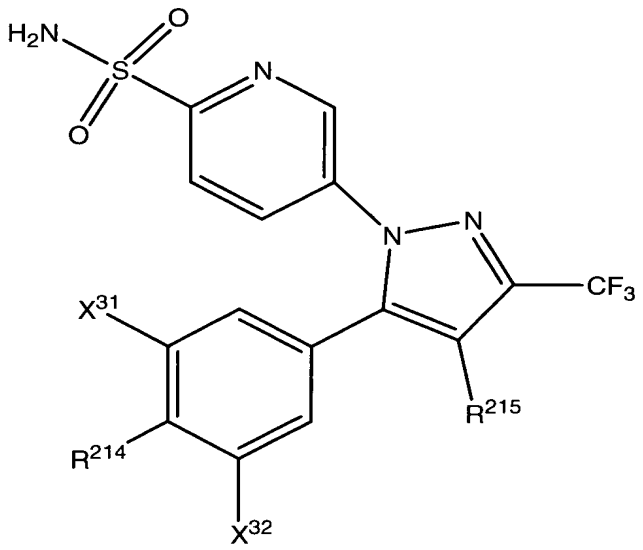
hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy, and alkylthio;

R^{211} and R^{212} are independently selected from the group consisting of hydroxyalkyl and hydrido but at least one of R^{211} and R^{212} is other than hydrido; and

R^{213} is selected from the group consisting of hydrido and fluoro.

[000139] Examples of prodrug compounds disclosed in U.S. 6,613,790 that are useful as Cox-2 inhibitors of the present invention include, but are not limited to, N-(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1- yl]benzenesulfonamide, N,N-bis(2-hydroxyethyl)-4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyraz ol-1-yl]benzenesulfonamide, or pharmaceuticaly-acceptable salts thereof.

[000140] Cox-2 selective inhibitors such as sulfamoylheleroaryl pyrazole compounds that are described in U.S. Patent No. 6,583,321 may serve as Cox-2 inhibitors of the present invention. Such sulfamoylheleroaryl pyrazole compounds have the formula shown below in formula **XXXXIII**:



XXXXIII

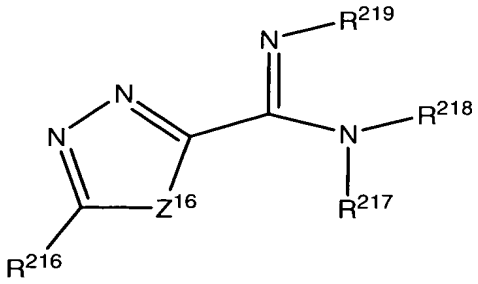
wherein:

R^{214} is furyl, thiazolyl or oxazolyl;

R^{215} is hydrogen, fluoro or ethyl; and

X^{31} and X^{32} are independently hydrogen or chloro.

[000141] Heteroaryl substituted amidinyl and imidazolyl compounds such as those described in U.S. Patent No. 6,555,563 are useful as Cox-2 selective inhibitors of the present invention. Such heteroaryl substituted amidinyl and imidazolyl compounds have the formula shown below in formula **XXXXIV**:



XXXXIV

wherein:

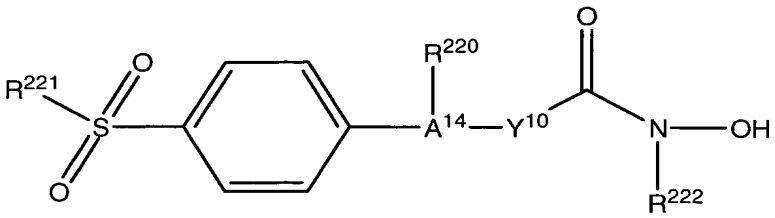
Z^{16} is O or S,

R^{216} is optionally substituted aryl,

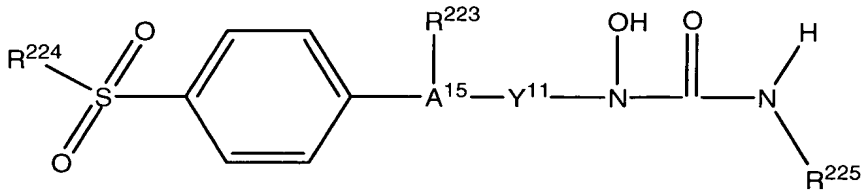
R^{217} is aryl optionally substituted with aminosulfonyl, and

R^{218} and R^{219} cooperate to form an optionally substituted 5-membered ring.

[000142] Materials that can serve as Cox-2 selective inhibitors of the present invention include substituted hydroxamic acid derivatives that are described in U.S. Patent Nos. 6,432,999, 6,512,121, and 6,515,014. These compounds also act as inhibitors of the lipoxygenase-5 enzyme. Such substituted hydroxamic acid derivatives have the general formulas shown below in formulas **XXXXV** and **XXXXVI**:



XXXXV



XXXXVI

[000143] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is selected from lower alkenylene and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000144] Pyrazole substituted hydroxamic acid derivatives described in U.S. Patent No. 6,432,999 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is pyrazolyl optionally substituted with a substituent selected from acyl, halo, hydroxyl, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkylene, lower alkenylene and lower alkynylene;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylmino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido, lower alkyl;

or a pharmaceutically-acceptable salt thereof.

[000145] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is a ring substiuent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isochiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A^{14} is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is lower alkylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is otionallv substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000146] Heterocyclo substituted hydroxamic acid derivatives described in U.S. Patent No. 6,512,121 may also have the formula shown above in formula **XXXXVI**, wherein:

A^{15} is a ring substituent selected from oxazolyl, furyl, pyrrolyl, thiazolyl, imidazolyl, isothiazolyl, isoxazolyl, cyclopentenyl, phenyl, and pyridyl; wherein A is optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarboryl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitto, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000147] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 have the formula shown above in formula **XXXXV**, wherein:

A^{14} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

Y^{10} is ethylene, isopropylene, propylene, butylene, lower alkenylene, and lower alkynylene;

R^{220} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{220} is optionally substituted at a substitutable position

with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{221} is selected from lower alkyl and amino; and

R^{222} is selected from hydrido, lower alkyl, phenyl, 5- and 6-membered heterocyclo and lower cycloalkyl; or a pharmaceutically-acceptable salt thereof.

[000148] Thiophene substituted hydroxamic acid derivatives described in U.S. Patent No. 6,515,014 may also have the formula shown above in formula **XXXXV**, wherein:

A^{15} is thienyl optionally substituted with a substituent selected from acyl, halo, hydroxy, lower alkyl, lower haloalkyl, oxo, cyano, nitro, carboxyl, lower alkoxy, aminocarbonyl, lower alkoxycarbonyl, lower carboxyalkyl, lower cyanoalkyl, and lower hydroxyalkyl;

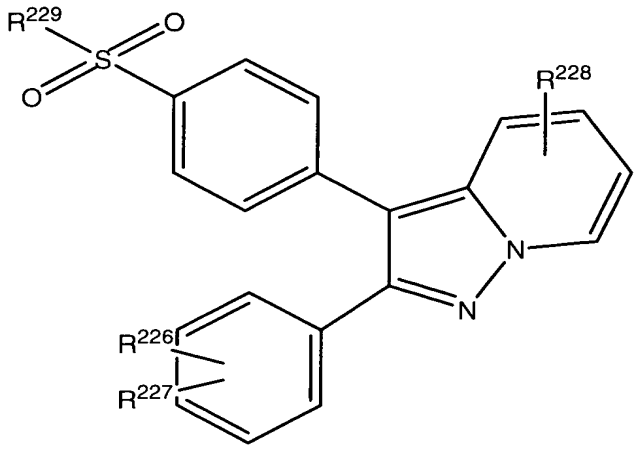
Y^{11} is selected from lower alkyl, lower alkenyl and lower alkynyl;

R^{223} is a substituent selected from 5- and 6-membered heterocyclo, lower cycloalkyl, lower cycloalkenyl and aryl selected from phenyl, biphenyl and naphthyl, wherein R^{223} is optionally substituted at a substitutable position with one or more substituents selected from lower alkyl, lower haloalkyl, cyano, carboxyl, lower alkoxycarbonyl, hydroxyl, lower hydroxyalkyl, lower haloalkoxy, amino, lower alkylamino, phenylamino, nitro, lower alkoxyalkyl, lower alkylsulfinyl, halo, lower alkoxy and lower alkylthio;

R^{224} is selected from lower alkyl and amino; and

R^{225} is selected from hydrido and alkyl; or a pharmaceutically-acceptable salt thereof.

[000149] Compounds that are useful as Cox-2 selective inhibitors of the present invention include pyrazolopyridine compounds that are described in U.S. Patent No. 6,498,166. Such pyrazolopyridine compounds have the formula shown below in formula **XXXXVII**:



XXXXVII

wherein:

R^{226} and R^{227} are independently selected from the group consisting of H, halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms;

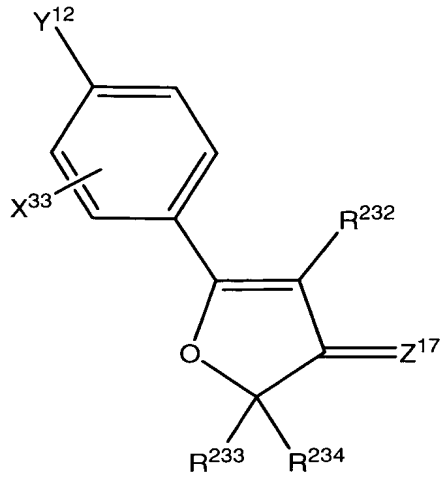
R^{228} is halogen, CN, CON R^{230} R^{231}, CO_2 H, CO_2 C_1 –C_6 alkyl, or $NHSO_2R^{230}$;

R^{229} is C_1 –C_6 alkyl or NH_2 ; and

R^{225} and R^{225} are independently selected from the group consisting of H, C_1 –C_6 alkyl, phenyl, phenyl substituted by one or more atoms or groups selected from the group consisting of halogen, C_1 –C_6 alkyl, C_1 –C_6 alkoxy, and C_1 –C_6 alkoxy substituted by one or more fluorine atoms,

or a pharmaceutically acceptable salt, solvate, ester, or salt or solvate of such ester thereof.

[000150] Materials that are useful as Cox-2 selective inhibitors of the present invention include 4,5-diaryl-3(2H)-furanone derivatives that are described in U.S. Patent No. 6,492,416. Such 4,5-diaryl-3(2H)-furanone derivatives have the formula shown below in formula **XXXXVIII**:



XXXXVIII

wherein:

X^{33} represents halo, hydrido, or alkyl;

Y^{12} represents alkylsulfonyl, aminosulfonyl, alkylsulfinyl, (N-acylamino)-sulfonyl, (N-alkylamino)sulfonyl, or alkylthio;

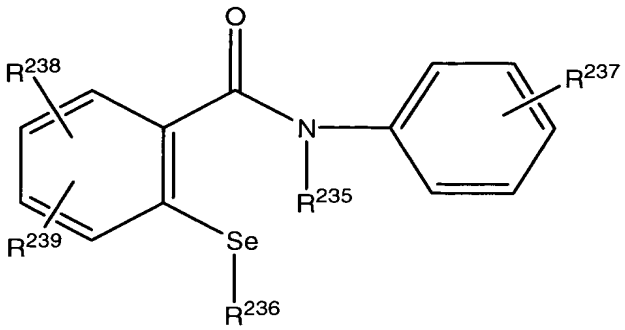
Z^{17} represents oxygen or sulfur atom;

R^{233} and R^{234} are selected independently from lower alkyl radicals;

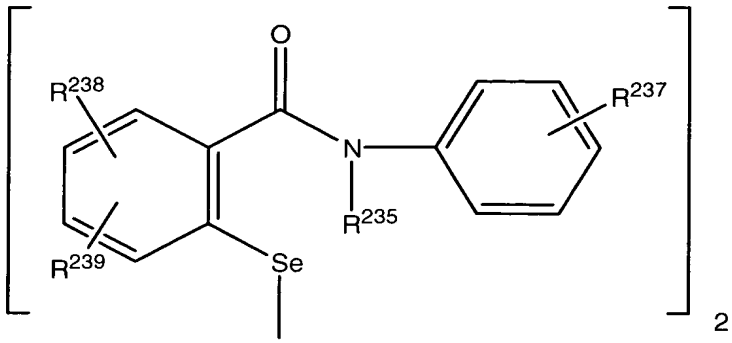
and R^{232} represents a substituted or non-substituted aromatic group of 5 to 10 atoms;

or a pharmaceutically-acceptable salt thereof.

[000151] Cox-2 selective inhibitors that can be used in the present invention include 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives that are described in U.S. Patent No. 6,492,416. Such 2-phenyl-1,2-benzisoselenazol-3(2H)-one derivatives and 2-phenylcarbomyl-phenylselenyl derivatives have the formulas shown below in formulas **XXXXIX** or **XXXXIX'**:



XXXXIX



XXXXIX'

wherein:

R^{235} is a hydrogen atom or an alkyl group having 1-3 carbon atoms;

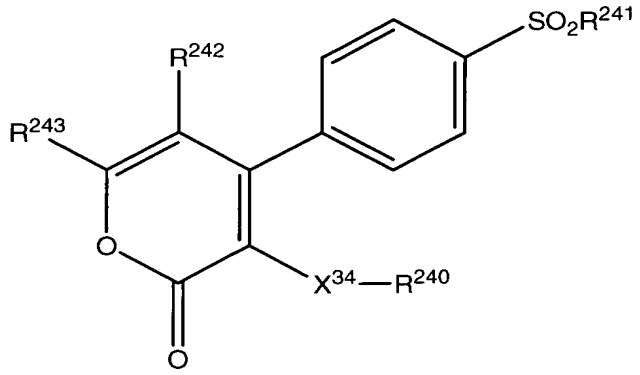
R^{236} is a hydrogen atom, a hydroxyl group, an organothiol group that is bound to the selenium atom by its sulfur atom, or R^{235} and R^{236} are joined to each other by a single bond;

R^{237} is a hydrogen atom, a halogen atom, an alkyl group having 1-3 carbon atoms, an alkoxyl group having 1-3 carbon atoms, a trifluoromethyl group, or a nitro group;

R^{238} and R^{239} are identical to or different from each other, and each is a hydrogen atom, a halogen atom, an alkoxyl group having 1-4 carbon atoms, a trifluoromethyl group, or R^{238} and R^{239} are joined to each other to form a methylenedioxy group,

a salt thereof, or a hydrate thereof.

[000152] Pyrones such as those disclosed in U.S. Patent No. 6,465,509 are also useful as Cox-2 inhibitors of the present invention. These pyrone compounds have the general formula shown below in formula **XXXXX:**



XXXXX

wherein:

X^{34} is selected from the group consisting of:

(a) a bond,

(b) --$(CH_2)_m$ --, wherein m 1 or 2,

(c) --C(O)--,

(d) --O--,

(e) --S--, and

(f) --$N(R^{244})$--;

R^{240} is selected from the group consisting of:

(a) C_1 –C_{10} alkyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: hydroxy, halo, C_1 –C_{10} alkoxy, C_1 – C_{10} alkylthio, and CN,

(b) phenyl or naphthyl, and

(c) heteroaryl, which is comprised of a monocyclic aromatic ring of 5 atoms having one hetero atom which is S, O or N, and optionally 1, 2, or 3 additional N atoms; or

a monocyclic ring of 6 atoms having one hetero atom which is N, and optionally 1, 2, or 3 additional N atoms, wherein groups (b) and (c) above are each optionally substituted with 1-3 substituents independently selected from the group consisting of: halo, C_1 –C_{10} alkoxy, C_1 –C_{10} alkylthio, CN, C_1 –C_{10} alkyl, optionally substituted to its maximum with halo, and N_3 ;

R^{241} is selected from the group consisting of

(a) C_1 –C_6 alkyl, optionally substituted to its maximum with halo,

(b) NH_2, and

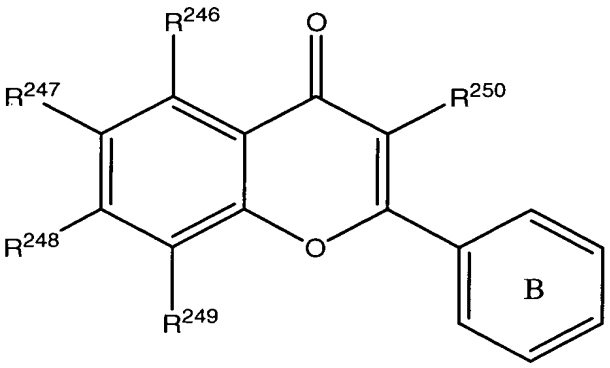
(c) $NHC(O)C_1$ –C_{10} alkyl, optionally substituted to its maximum with halo;

R^{242} and R^{243} are each independently selected from the group consisting of: hydrogen, halo, and C_1 –C_6 alkyl, optionally substituted to its maximum with halo; and

R^{244} is selected from the group consisting of: hydrogen and C_1 –C_6 alkyl, optionally substituted to its maximum with halo.

[000153] Examples of pyrone compounds that are useful as Cox-2 selective inhibitors of the present invention include, but are not limited to:
4-(4-Methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
3-(4-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
3-(3-Fluorophenyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Difluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Fluoromethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenylthio-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-phenoxy-pyran-2-one,
6-Methyl-4-(4-methylsulfonyl)phenyl-3-pyridin-3-yl-pyran-2-one,
3-Isopropylthio-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl)-3-phenylthio-6-trifluoromethyl-pyran-2-one,
3-Isopropylthio-4-(4-methylsulfonyl)phenyl-6-trifluoromethyl-pyran-2-one,
4-(4-Methylsulfonyl)phenyl-3-phenyl-6-(2,2,2-trifluoroethyl)-pyran-2-one,
and
3-(3-Hydroxy-3-methylbutyl)-6-methyl-4-(4-methylsulfonyl)phenyl-pyran-2-one.

[000154] Organically synthesized or purified from plant sources, free-B-ring flavanoids such as those described in U.S. Published Application No. 2003/0165588, are useful as Cox-2 selective inhibitors of the present invention. Such free-B-ring flavanoids have the general structure shown in formula **XXXXXI**:

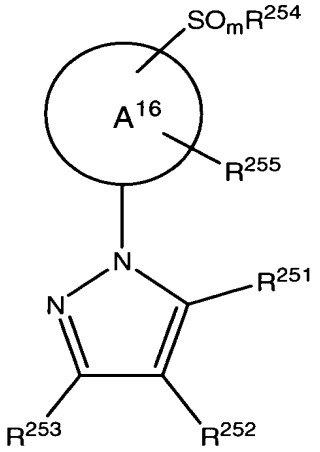


XXXXXI

wherein:

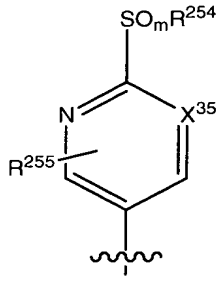
R^{246}, R^{247}, R^{248}, R^{249}, and R^{250} are independently selected from the group consisting of: --H, --OH, --SH, --OR, --SR, $--NH_2$, $--NHR^{245}$, $--N(R^{245})_2$, $--N(R^{245})_3{}^+X^{35-}$, a carbon, oxygen, nitrogen or sulfur, glycoside of a single or a combination of multiple sugars including, aldopentoses, methyl-aldopentose, aldohexoses, ketohexose and their chemical derivatives thereof; wherein R^{245} is an alkyl group having between 1-10 carbon atoms; and X^{35} is selected from the group of pharmaceutically acceptable counter anions including, hydroxyl, chloride, iodide, sulfate, phosphate, acetate, fluoride and carbonate.

[000155] Heterocyclo-alkylsulfonyl pyrazoles such as those described in European Patent Application No. EP 1312367 are useful as Cox-2 selective inhibitors of the present invention. Such heterocyclo-alkylsulfonyl pyrazoles have the general formula shown below in formula **XXXXXII**:



XXXXXII

or a pharmaceutically acceptable salt thereof, wherein:
the ring of the formula (R^{255})-A-(SO_mR^{254}) is selected from the group consisting of:



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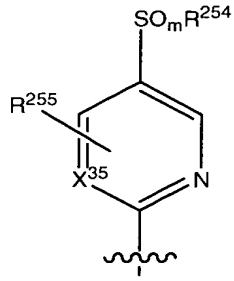

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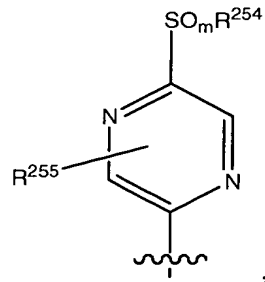

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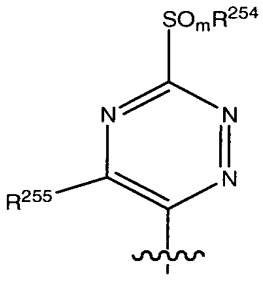

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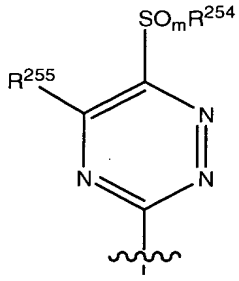
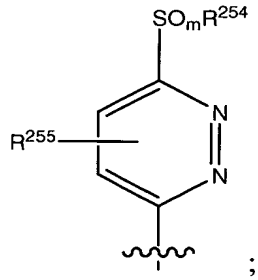


, and


;

m is 0, 1 or 2;

X^{35} is $>CR^{255}$ or >N;

R^{251} is a radical selected from the group consisting of H, NO_2, CN, (C_1 – C_6)alkyl, (C_1 –C_6)alkyl-SO_2-, (C_6 –C_{10})aryl-SO_2-, H-(C=O)-, (C_1 –C_6)alkyl-(C=O)-, (C_1 –C_6)alkyl-)-(C=O)-, (C_1 –C_9)heteroaryl-(C=O)-, (C_1 – C_9)heterocyclyl-(C=O)-, H_2N-(C=O)-, (C_1 –C_6)alkyl-NH-(C=O)-, [(C_1 – C_6)alkyl]$_2$-N-(C=O)-, [(C_6 –C_{10})aryl]$_2$-NH-(C=O)-, [(C_1 –C_6)alkyl]-[((C_6 – C_{10})aryl-N]-(C=O)-, HO-NH-(C=O)-, and (C_1 –C_6)alkyl-O-NH-(C=O)-;

R^{252} is a radical selected from the group consisting of H, -NO_2, -CN, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_1-C_9)heteroaryl, (C_1-C_9)heterocyclyl, (C_1-C_6)alkyl-O-, (C_3-C_7)cycloalkyl-O-, (C_6-C_{10})aryl-O-, (C_1 -C_9)heteroaryl-O-, (C_6 -C_9)heterocyclyl-O-, H-(C=O)-, (C_1-C_6)alkyl-(C=O)-, (C_3-C_7)cycloalkyl-(C=O)-, (C_6-C_{10})aryl-(C=O)-, (C_1-C_9)heteroaryl-(C=O)-, (C_1-C_9)heterocyclyl-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, (C_3-C_7)cycloalkyl-O-(C=O)-, (C_6-C_{10})aryl-O-(C=O)-, (C_1-C_9)heteroaryl-O-(C=O)-, (C_1-C_9)heterocyclyl-O-(C=O)-, (C_1-C_6)alkyl-(C=O)-O-, (C_3-C_7)cycloalkyl-(C=O)-O-, (C_6-C_{10})aryl-(C=O)-O-, (C_1-C_9)heteroaryl-(C=O)-O-, (C_1-C_9)heterocyclyl-(C=O)-O-, (C_1-C_6)alkyl-(C=O)-NH-, (C_3-C_7)cycloalkyl-(C=0)-NH-, (C_6-C_{10}aryl-(C=O)-NH-. (C_1-C_9)heteroaryl-(C=O)-

NH-, (C_1-C_9)heterocyclyl-(C=O)-NH-, (C_1-C_6)alkyl-O-(C=O)-NH-, (C_1-C_6)alkyl-NH, [(C_1-C_6)alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-. [(C_3-C_7)cycloalkyl]$_2$-N-, [(C_6-C_{10})aryl]-NH-, [(C_6-C_{10})aryl]$_2$-N-, [(C_1–C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, [(C_1-C_9)heteroaryl]-NH-, [(C_1-C_9)heteroaryl]$_2$-N-, [(C_1-C_9)heterocycly]-NH-, [(C_1-C_9)heterocyclyl]$_2$-N-, H_2N-(C=O)-, HO-NH-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, [(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_3-C_7)cycloalkyl]-NH-(C=O)-, [(C_3-C_7)cycloalkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_6-C_{10}aryl]$_2$-N-(C=O)-, [(C_1-C $_6$)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, [(C_1-C_9)heteroaryl]-NH-(C=O)-, [(C_1-C_9)heferoaryl]$_2$-N-(O=O)-, [(C_1-C_9)heterocyclyl]-NH-(C=O)-, (C_1–C_6)alkyl-S- and (C_1-C_6)alkyl optionally substituted by one -OH substituent or by one to four fluoro substituents;

R^{253} is a saturated (3- to 4-membered)-heterocyclyl ring radical; or a saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical orsaid saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may optionally contain one to four ring heteroatoms independently selected Irom the groups consisting of -N=, -NH-, -O-. and -S-;

wherein said saturated (3- to 4-membered)-heterooyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-nembered)-heterocyclyl ring radical; may optionally be substituted on any ring carbon atom by one to three substituents per ring independently selected from the group consisting of halo, -OH, -CN, -NO_2, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, (C_3-C_7)cycloalkyl, (C_6-C_{10})aryl, (C_2-C_9)hetorocyclyl, (C_1–C_6)alkyl-O-, H-(C=0)-, (C_1-C_6)alkyl-(C=O)-, HO-(C=O)-, (C_1-C_6)alkyl-O-(C=O)-, -NH_2, (C_1-C_6)alkyl-NH-, [(C_1-C_6) alkyl]$_2$-N-, (C_3-C_7)cycloalkyl-NH-, (C_6-C_{10})aryl-NH-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-, (C_1-C_9)heteroaryl-NH-, H_2N-(C=O)-[(C_1-C_6)alkyl]-NH-(C=O)-, [(C_1-C_6)alkyl]$_2$-N-(C=O)-, [(C_6-C_{10})aryl]-NH-(C=O)-, [(C_1-C_6)alkyl]-[((C_6-C_{10})aryl)-N]-(C=O)-, (C_1-C_6)alkyl-O-NH-(C=O)-, (C_1-C_6)alkyl-(C=O)-HN-, (C_1-C_6)alkyl-(C=O)-[(C_1-C_6)alkyl-N]-, -SH, (C_1-C_6)alkyl-S-,

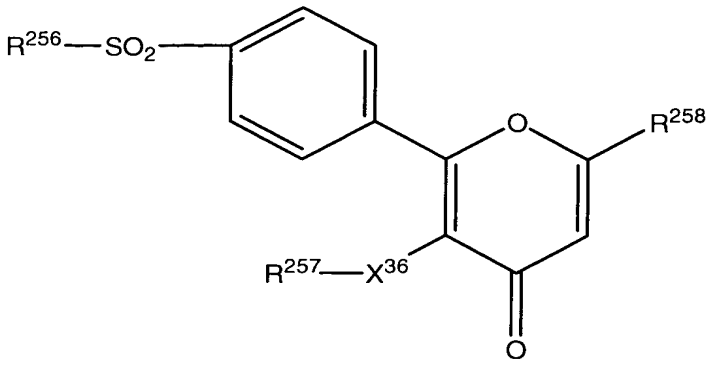
$(C_1$-$C_6)$alkyl-(S=0)-, $(C_1$-$C_6)$alkyl-SO_2- and $(C_1$-$C_6)$alkyl optionally substituted with one to fourfluoro moieties;

wherein said saturated (3- to 4-membered)-heterocyclyl ring radical; or said saturated, partially saturated or aromatic (7- to 9-membered)-heterocyclyl ring radical; may also optionally be substituted on any ring nitrogen atom by one to three substituents per ring independently selected from the group consisting of $(C_3$-$C_7)$cyoloalkyl, $(C_6$-$C_{10})$aryl, $(C_2$-$C_9)$heterocyclyl, H-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, H_2N-(C=O)-, [$(C_1$-$C_6)$alkyl]-NH-(C=O)-, [$(C_1$-$C_6)$alkyl]$_2$-N-(C=O)-, [$(C_6$-$C_{10})$aryl]-NH-(C=O)-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-(C=O)-, $(C_1$ –$C_6)$alkyl-O-NH-(C=O)-, and $(C_1$-$C_6)$alkyl optionally substituted with one to four fluoro moieties;

R^{254} is an $(C_1$-$C_6)$alkyl radical optionally substituted by one to four fluoro substituents; and

R^{255} is a radical selected from the group consisting of H, halo, -OH, $(C_1$-$C_6)$alkyl-O-, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_3$-$C_7)$cycloalkyl, -CN, H-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-, $(C_1$-$C_6)$alkyl-(C=O)-O-, HO-(C=O)-, $(C_1$-$C_6)$alkyl-O-(C=O)-, $(C_1$-$C_6)$alkyl-NH-. [$(C_1$-$C_6)$alkyl]$_2$-N-, $(C_3$-$C_7)$cycloalkyl-NH-, $(C_6$-$C_{10})$aryl-NH-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-, $(C_1$-$C_9)$heteroaryl-NH-, H_2N-(C=O)-, $(C_1$-$C_6)$alkyl-NH-(C=O)-. [$(C_1$-$C_6)$alkyl]$_2$-N-(C=O)-, $(C_6$-$C_{10})$aryl-(C=O)-, [$(C_1$-$C_6)$alkyl]-[($(C_6$-$C_{10})$aryl)-N]-(C=O)-, $(C_1$-$C_6)$alkyl-O-NH-(C=O)-, $(C_1$-$C_6)$alkyl-S-, and $(C_1$-$C_6)$alkyl optionally substituted by one to four fluoro substituents.

[000156] 2-phenylpyran-4-one derivatives such as those described in U.S. Patent No. 6,518,303 are also useful as Cox-2 selective inhibitors of the present invention. Such 2-phenylpyran-4-one derivatives have the general formula shown below in formula **XXXXXIII**:



XXXXXIII

wherein:

R^{256} represents an alkyl or $-NR^{259}$ R^{260} group, wherein R^{259} and R^{260} each independently represents a hydrogen atom or an alkyl group;

R^{257} represents an alkyl, C_3 $-C_7$ cycloalkyl, naphthyl, tetrahydronaphthyl or indanyl group, or a phenyl group which may be unsubstituted or substituted by one or more halogen atoms or alkyl, trifluoromethyl, hydroxy, alkoxy, methylthio, amino, mono- or dialkylamino, hydroxyalkyl or hydroxycarbonyl groups;

R^{258} represents a methyl, hydroxymethyl, alkoxymethyl, C_3 $-C_7$ cycloalkoxymethyl, benzyloxymethyl, hydroxycarbonyl, nitrile, trifluoromethyl or difluoromethyl group or a CH_2 -- R^{261} group wherein R^{261} represents an alkyl group; and

X^{36} represents a single bond, an oxygen atom, a sulfur atom or a methylene group;

or a pharmaceutically acceptable salt thereof.

[000157] Examples of 2-phenylpyran-4-one derivatives useful in the present invention include, but are not limited to:

3-(4-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(4-bromophenyl)-2-(4-methylsulfonylphenyl)-6-methylpyran-4-one,

3-(2,4-difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3,4-dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,

3-(3-chloro-4-methylphenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one ,

2-(4-methanesulfonylphenyl)-6-methyl-3-phenoxypyran-4-one,
3-(4-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-fluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2-chlorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
2-(4-methanesulfonylphenyl)-6-methyl-3-(4-methylphenoxy)pyran-4-one,
3-(2,4-difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one,
3-(2,5-difluorophenoxy)-2-(methanesulfonylphenyl)-6-methylpyran-4-one,
3-(4-chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methoxymethylpyran-4-one,
3-(4-chlorophenyl)-6-difluoromethyl-2-(4-methanesulfonylphenyl)pyran-4-one,
and pharmaceutically acceptable salts thereof.

[000158] Cox-2 selective inhibitors that are useful in the subject method and compositions can include the compounds that are described in U.S. Patent No. 6,472,416 (sulfonylphenylpyrazoles); U.S. Patent No. 6,451,794 (2,3-diaryl-pyrazolo[1,5-b]pyridazines); U.S. Patent Nos. 6,169,188, 6,020,343, and 5,981,576 ((methylsulfonyl)phenyl furanones); U.S. Patent No. 6,222,048 (diaryl-2-(5H)-furanones); U.S. Patent No. 6,057,319 (3,4-diaryl-2-hydroxy-2,5-dihydrofurans); U.S. Patent No. 6,046,236 (carbocyclic sulfonamides); U.S. Patent Nos. 6,002,014 and 5,945,539 (oxazole derivatives); and U.S. Patent Nos. 6,359,182 and 6,538,116 (C-nitroso compounds).

[000159] Examples of specific compounds that are useful as Cox-2 selective inhibitors include, without limitation:

a1) 8-acetyl-3-(4-fluorophenyl)-2-(4-methylsulfonyl)phenyl-imidazo(1,2-a)pyridine;

a2) 5,5-dimethyl-4-(4-methylsulfonyl)phenyl-3-phenyl-2-(5H)-furanone;

a3) 5-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole;

a4) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-1-phenyl-3-(trifluoromethyl)pyrazole;

a5) 4-(5-(4-chlorophenyl)-3-(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide

a6) 4-(3,5-bis(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a7) 4-(5-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)benzenesulfonamide;

a8) 4-(3,5-bis(4-methoxyphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a9) 4-(5-(4-chlorophenyl)-3-(4-methylphenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

a10) 4-(5-(4-chlorophenyl)-3-(4-nitrophenyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b1) 4-(5-(4-chlorophenyl)-3-(5-chloro-2-thienyl)-1H-pyrazol-1-yl)benzenesulfonamide;

b2) 4-(4-chloro-3,5-diphenyl-1H-pyrazol-1-yl)benzenesulfonamide

b3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b4) 4-[5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b5) 4-[5-(4-fluorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b6) 4-[5-(4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b7) 4-[5-(4-chlorophenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b8) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b9) 4-[4-chloro-5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

b10) 4-[3-(difluoromethyl)-5-(4-methylphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c1) 4-[3-(difluoromethyl)-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c2) 4-[3-(difluoromethyl)-5-(4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c3) 4-[3-cyano-5-(4-fluorophenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c4) 4-[3-(difluoromethyl)-5-(3-fluoro-4-methoxyphenyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c6) 4-[4-chloro-5-phenyl-1H-pyrazol-1-yl]benzenesulfonamide;

c7) 4-[5-(4-chlorophenyl)-3-(hydroxymethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c8) 4-[5-(4-(N,N-dimethylamino)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

c9) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

c10) 4-[6-(4-fluorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d1) 6-(4-fluorophenyl)-7-[4-(methylsulfonyl)phenyl]spiro[3.4]oct-6-ene;

d2) 5-(3-chloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d3) 4-[6-(3-chloro-4-methoxyphenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d4) 5-(3,5-dichloro-4-methoxyphenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d5) 5-(3-chloro-4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hept-5-ene;

d6) 4-[6-(3,4-dichlorophenyl)spiro[2.4]hept-5-en-5-yl]benzenesulfonamide;

d7) 2-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d8) 2-(2-chlorophenyl)-4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)thiazole;

d9) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-methylthiazole;

d10) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e1) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(2-thienyl)thiazole;

e2) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-benzylaminothiazole;

e3) 4-(4-fluorophenyl)-5-(4-methylsulfonylphenyl)-2-(1-propylamino)thiazole;

e4) 2-[(3,5-dichlorophenoxy)methyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]thiazole;

e5) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethylthiazole;

e6) 1-methylsulfonyl-4-[1,1-dimethyl-4-(4-fluorophenyl)cyclopenta-2,4-dien-3-yl]benzene;

e7) 4-[4-(4-fluorophenyl)-1,1-dimethylcyclopenta-2,4-dien-3-yl]benzenesulfonamide;

e8) 5-(4-fluorophenyl)-6-[4-(methylsulfonyl)phenyl]spiro[2.4]hepta-4,6-diene;

e9) 4-[6-(4-fluorophenyl)spiro[2.4]hepta-4,6-dien-5-yl]benzenesulfonamide;

e10) 6-(4-fluorophenyl)-2-methoxy-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f1) 2-bromo-6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-pyridine-3-carbonitrile;

f2) 6-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyl-pyridine-3-carbonitrile;

f3) 4-[2-(4-methylpyridin-2-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f4) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f5) 4-[2-(2-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

f6) 3-[1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f7) 2-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f8) 2-methyl-4-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f9) 2-methyl-6-[1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazol-2-yl]pyridine;

f10) 4-[2-(6-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g1) 2-(3,4-difluorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

g2) 4-[2-(4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g3) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-methyl-1H-imidazole;

g4) 2-(4-chlorophenyl)-1-[4-(methylsulfonyl)phenyl]-4-phenyl-1H-imidazole;

g5) 2-(4-chlorophenyl)-4-(4-fluorophenyl)-1-[4-(methylsulfonyl)phenyl]-1H-imidazole;

g6) 2-(3-fluoro-4-methoxyphenyl)-1-[4-(methylsulfonyl)phenyl-4-(trifluoromethyl)-1H-imidazole;

g7) 1-[4-(methylsulfonyl)phenyl]-2-phenyl-4-trifluoromethyl-1H-imidazole;

g8) 2-(4-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

g9) 4-[2-(3-chloro-4-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

g10) 2-(3-fluoro-5-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-(trifluoromethyl)-1H-imidazole;

h1) 4-[2-(3-fluoro-5-methylphenyl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

h2) 2-(3-methylphenyl)-1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazole;

h3) 4-[2-(3-methylphenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h4) 1-[4-(methylsulfonyl)phenyl]-2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazole;

h5) 4-[2-(3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h6) 4-[2-phenyl-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h7) 4-[2-(4-methoxy-3-chlorophenyl)-4-trifluoromethyl-1H-imidazol-1-yl]benzenesulfonamide;

h8) 1-allyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

h9) 4-[1-ethyl-4-(4-fluorophenyl)-5-(trifluoromethyl)-1H-pyrazol-3-yl]benzenesulfonamide;

i1) N-phenyl-[4-(4-luorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetamide;

i2) ethyl [4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazol-1-yl]acetate;

i3) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-1H-pyrazole;

i4) 4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-1-(2-phenylethyl)-5-(trifluoromethyl)pyrazole;

i5) 1-ethyl-4-(4-fluorophenyl)-3-[4-(methylsulfonyl)phenyl]-5-(trifluoromethyl)-1H-pyrazole;

i6) 5-(4-fluorophenyl)-4-(4-methylsulfonylphenyl)-2-trifluoromethyl-1H-imidazole;

i7) 4-[4-(methylsulfonyl)phenyl]-5-(2-thiophenyl)-2-(trifluoromethyl)-1H-imidazole;

i8) 5-(4-fluorophenyl)-2-methoxy-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i9) 2-ethoxy-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

i10) 5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-2-(2-propynyloxy)-6-(trifluoromethyl)pyridine;

j1) 2-bromo-5-(4-fluorophenyl)-4-[4-(methylsulfonyl)phenyl]-6-(trifluoromethyl)pyridine;

j2) 4-[2-(3-chloro-4-methoxyphenyl)-4,5-difluorophenyl]benzenesulfonamide;

j3) 1-(4-fluorophenyl)-2-[4-(methylsulfonyl)phenyl]benzene;

j4) 5-difluoromethyl-4-(4-methylsulfonylphenyl)-3-phenylisoxazole;

j5) 4-[3-ethyl-5-phenylisoxazol-4-yl]benzenesulfonamide;

j6) 4-[5-difluoromethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j7) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

j8) 4-[5-methyl-3-phenyl-isoxazol-4-yl]benzenesulfonamide;

j9) 1-[2-(4-fluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

j10) 1-[2-(4-fluoro-2-methylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k1) 1-[2-(4-chlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k2) 1-[2-(2,4-dichlorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k3) 1-[2-(4-trifluoromethylphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k4) 1-[2-(4-methylthiophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k5) 1-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k6) 4-[2-(4-fluorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k7) 1-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]-4-(methylsulfonyl)benzene;

k8) 4-[2-(4-chlorophenyl)-4,4-dimethylcyclopenten-1-yl]benzenesulfonamide;

k9) 4-[2-(4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

k10) 4-[2-(4-chlorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l1) 1-[2-(4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l2) 1-[2-(2,3-difluorophenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l3) 4-[2-(3-fluoro-4-methoxyphenyl)cyclopenten-1-yl]benzenesulfonamide;

l4) 1-[2-(3-chloro-4-methoxyphenyl)cyclopenten-1-yl]-4-(methylsulfonyl)benzene;

l5) 4-[2-(3-chloro-4-fluorophenyl)cyclopenten-1-yl]benzenesulfonamide;

l6) 4-[2-(2-methylpyridin-5-yl)cyclopenten-1-yl]benzenesulfonamide;

l7) ethyl 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl) phenyl]oxazol-2-yl]-2-benzyl-acetate;

l8) 2-[4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazol-2-yl]acetic acid;

l9) 2-(*tert*-butyl)-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]oxazole;

l10) 4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl]-2-phenyloxazole;

m1) 4-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]oxazole; and

m2) 4-[5-(3-fluoro-4-methoxyphenyl)-2-trifluoromethyl-4-oxazolyl]benzenesulfonamide.

m3) 6-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m4) 6-chloro-7-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m5) 8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m6) 6-chloro-7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m7) 6-chloro-8-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m8) 2-trifluoromethyl-3H-naphthopyran-3-carboxylic acid ;

m9) 7-(1,1-dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

m10) 6-bromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n1) 8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n2) 6-trifluoromethoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n3) 5,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n4) 8-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n5) 7,8-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n6) 6,8-bis(dimethylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n7) 7-(1-methylethyl)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n8) 7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n9) 6-chloro-7-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

n10) 6-chloro-8-ethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o1) 6-chloro-7-phenyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o2) 6,7-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o3) 6,8-dichloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o4) 2-trifluoromethyl-3H-naptho[2,1-b]pyran-3-carboxylic acid;

o5) 6-chloro-8-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o6) 8-chloro-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o7) 8-chloro-6-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o8) 6-bromo-8-chloro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o9) 8-bromo-6-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

o10) 8-bromo-6-methyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p1) 8-bromo-5-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p2) 6-chloro-8-fluoro-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p3) 6-bromo-8-methoxy-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p4) 6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p5) 6-[(dimethylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p6) 6-[(methylamino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p7) 6-[(4-morpholino)sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p8) 6-[(1,1-dimethylethyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p9) 6-[(2-methylpropyl)aminosulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

p10) 6-methylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q1) 8-chloro-6-[[(phenylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q2) 6-phenylacetyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q3) 6,8-dibromo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q4) 8-chloro-5,6-dimethyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q5) 6,8-dichloro-(*S*)-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q6) 6-benzylsulfonyl-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q7) 6-[[N-(2-furylmethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q8) 6-[[N-(2-phenylethyl)amino]sulfonyl]-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q9) 6-iodo-2-trifluoromethyl-2H-1-benzopyran-3-carboxylic acid;

q10) 7-(1,1-dimethylethyl)-2-pentafluoroethyl-2H-1-benzopyran-3-carboxylic acid;

r1) 5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methyl-sulphonyl-2(5H)-fluranone;

r2) 6-chloro-2-trifluoromethyl-2H-1-benzothiopyran-3-carboxylic acid;

r3) 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r4) 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r5) 4-[5-(3-fluoro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide;

r6) 3-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r7) 2-methyl-5-[1-[4-(methylsulfonyl)phenyl]-4-trifluoromethyl-1H-imidazol-2-yl]pyridine;

r8) 4-[2-(5-methylpyridin-3-yl)-4-(trifluoromethyl)-1H-imidazol-1-yl]benzenesulfonamide;

r9) 4-[5-methyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

r10) 4-[5-hydroxymethyl-3-phenylisoxazol-4-yl]benzenesulfonamide;

s1) [2-trifluoromethyl-5-(3,4-difluorophenyl)-4-oxazolyl]benzenesulfonamide;

s2) 4-[2-methyl-4-phenyl-5-oxazolyl]benzenesulfonamide; or

s3) 4-[5-(3-fluoro-4-methoxyphenyl-2-trifluoromethyl)-4-oxazolyl]benzenesulfonamide;

or a pharmaceutically acceptable salt or prodrug thereof.

[000160] Cox-2 inhibitors that are useful in the methods and compositions of present invention can be supplied by any source as long

as the Cox-2 inhibitor is pharmaceutically acceptable. Likewise, Cox-2 inhibitors that are useful in the compositions and methods of present invention can be synthesized, for example, according to the description in Example 1. Several Cox-2 inhibitors that are suitable for use with the compositions and methods of the present invention may be synthesized by the methods described in, for example, in U.S. Patent No. 5,466,823 to Talley, *et al.*

[000161] Preferred Cox-2 selective inhibitor compounds are those compounds selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, etoricoxib, meloxicam, rofecoxib, lumiracoxib, RS 57067, T-614, BMS-347070 (Bristol Meyers Squibb, described in U.S. Patent No. 6,180,651), JTE-522 (Japan Tabacco), S-2474 (Shionogi), SVT-2016, CT-3 (Atlantic Pharmaceutical), ABT-963 (Abbott), SC-58125 (GD Searle), nimesulide, flosulide, NS-398 (Taisho Pharmaceutical), L-745337 (Merck), RWJ-63556, L-784512 (Merck), darbufelone (Pfizer), CS-502 (Sankyo), LAS-34475 (Almirall Prodesfarma), LAS-34555 (Almirall Prodesfarma), S-33516 (Servier), SD-8381 (Pharmacia, described in U.S. Patent No. 6,0340256), MK-966 (Merck), L-783003 (Merck), T-614 (Toyama), D-1376 (Chiroscience), L-748731 (Merck), CGP-28238 (Novartis), BF-389 (Biofor/Scherer), GR-253035 (Glaxo Wellcome), prodrugs of any of them, and mixtures thereof.

[000162] More preferred is that the Cox-2 selective inhibitor is selected from the group consisting of celecoxib, parecoxib, deracoxib, valdecoxib, lumiracoxib, etoricoxib, rofecoxib, prodrugs of any of them, and mixtures thereof.

[000163] Even more preferred still is that the Cox-2 selective inhibitor is celecoxib.

[000164] Cox-2 inhibitors that are useful in the methods and compositions and methods of present invention can be supplied by any source as long as the Cox-2 inhibitor is pharmaceutically acceptable.

[000165] Various classes of Cox-2 inhibitors useful in the present invention can be prepared as follows. Pyrazoles can be prepared by

methods described in WO 95/15316. Pyrazoles can further be prepared by methods described in WO 95/15315. Pyrazoles can also be prepared by methods described in WO 96/03385.

[000166] Thiophene analogs useful in the present invention can be prepared by methods described in WO 95/00501. Preparation of thiophene analogs is also described in WO 94/15932.

[000167] Oxazoles useful in the present invention can be prepared by the methods described in WO 95/00501. Preparation of oxazoles is also described in WO 94/27980.

[000168] Isoxazoles useful in the present invention can be prepared by the methods described in WO 96/25405.

[000169] Imidazoles useful in the present invention can be prepared by the methods described in WO 96/03388. Preparation of imidazoles is also described in WO 96/03387.

[000170] Cyclopentene Cox-2 inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 5,344,991. Preparation of cyclopentene Cox-2 inhibitors is also described in WO 95/00501.

[000171] Terphenyl compounds useful in the present invention can be prepared by the methods described in WO 96/16934.

[000172] Thiazole compounds useful in the present invention can be prepared by the methods described in WO 96/03,392.

[000173] Pyridine compounds useful in the present invention can be prepared by the methods described in WO 96/03392. Preparation of pyridine compounds is also described in WO 96/24,585.

[000174] Benzopyranopyrazolyl compounds useful in the present invention can be prepared by the methods described in WO 96/09304.

[000175] Chromene compounds useful in the present invention can be prepared by the methods described in WO 98/47890. Preparation of chromene compounds is also described in WO 00/23433. Chromene compounds can further be prepared by the methods described in U.S.

Patent No. 6,077,850. Preparation of chromene compounds is further described in U.S. Patent No. 6,034,256.

[000176] Arylpyridazinones useful in the present invention can be prepared by the methods described in WO 00/24719. Preparation of arylpyridazinones is also described in WO 99/10332. Arylpyridazinones can further be prepared by the methods described in WO 99/10331.

[000177] 5-Alkyl-2-arylaminophenylacetic acids and derivatives useful in the present invention can be prepared by the methods described in WO 99/11605.

[000178] Diarylmethylidenefuran derivative Cox-2 selective inhibitors useful in the present invention can be prepared by the methods described in U.S. Patent No. 6,180,651.

[000179] The celecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,466,823.

[000180] The valdecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,633,272.

[000181] The parecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,932,598.

[000182] The rofecoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,474,995.

[000183] The deracoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,521,207.

[000184] The etoricoxib used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 98/03484.

[000185] The meloxicam used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,233,299.

[000186] The compound 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 5,994,381.

[000187] The compound 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 00/24719.

[000188] The compound 2-(3,5-difluorophenyl)-3-[4-(methylsulfonyl)phenyl]-2-cyclopenten-1-one used in the compositions and methods of the present invention can be prepared in the manner set forth in EP 863134.

[000189] The compound 2-[(2-chloro-6-fluorophenyl)amino]-5-methyl-benzeneacetic acid used in the compositions and methods of the present invention can be prepared in the manner set forth in WO 99/11605.

[000190] The compound N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 4,885,367.

[000191] The compound (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone used in the compositions and methods of the present invention can be prepared in the manner set forth in U.S. Patent No. 6,180,651.

[000192] Cox-2 inhibitors can also be isolated and purified from natural sources. Cox-2 inhibitors should be of a quality and purity that is conventional in the trade for use in pharmaceutical products.

[000193] An optional component of the present invention is an otic agent that is administered to a subject in combination with a Cox-2 inhibitor.

[000194] As used herein, the term "otic agent" refers to any compound recognized as having a therapeutic effect on an otic disorder or an otic disorder agent, whether *in vivo* or *in vitro*, over any duration of time other than a chemical that is an inhibitor of the Cox-2 enzyme. This effect can occur via bacterial and/or viral growth suppression, inflammation reduction, eustachian tube dilation, or by any other mechanism.

[000195] Examples of preferred classes of otic agents capable of treating or preventing the symptoms of an otic disorder in combination with a Cox-2 inhibitor include, but are not limited to, one or more of antibiotics, antifungals, corticosteroids, astrigents, anticholinergics, antiseptics, antivirals, decongestants, antihistamines and anaesthetics.

[000196] For purposes of the present invention, combinations of a Cox-2 inhibitor and an otic agent, such as an antibiotic, provides an effective treatment therapy for several otic disorders. The term "antibacterial" or "antibiotic" used interchangeably herein, means any chemical of natural or synthetic origin which has the effect to kill or inhibit or suppress the growth of biological cells. Examples of antibacterial agents encompassed by the combination methods and compositions of the present invention include those antibiotics and antibiotic classes set forth in table 3 below. See, Todar, K., *Todar's Textbook of Bacteriology*, University of Wisconsin-Madison, Department of Bacteriology (2002) and *The Merck Manual, Sec. 13. Chap. 153.*, "Antibacterial Drugs," 17th Edition (1999).

Table 3

Table 3: Classes and Examples of Antibiotic Otic Agents	
Antibiotic Class	Examples
Beta-lactams - penicillins	Penicillin G, Penicillin V, Procaine, Benzathine, Cloxacillin, Dicloxacillin, Methicillin, Nafcillin, Oxacillin, Azlocillin, Carbenicillin, Piperacillin, Piperacillin plus Tazobactam, Ticarcillin and Mezlocillin

Table 3: Classes and Examples of Antibiotic Otic Agents	
Antibiotic Class	Examples
Beta-lactams - cephalosporins	First-generation Cefadroxil, Cefazolin, Cephalexin, Cephalothin, Cephapirin and Cephradine Second-generation Cefaclor, Cefamandole, Cefmetazole Cefonicid, Cefotetan, Cefoxitin, Cefprozil, Cefuroxime and Loracarbef Third-generation Cefepime, Cefixime, Cefoperazone, Cefotaxime, Cefpodoxime, Ceftazidime, Ceftibuten, Ceftizoxime and Ceftriaxone
Other Beta-lactams	Meropenem, Sulbactam, Tazobactam
Semisynthetic penicillin	Ampicillin, Ampicillin plus Sulbactam, Amoxycillin, Amoxicillin, Amoxicillin plus clavulanate and Bacampicillin
Clavulanic Acid	Clavamox (clavulanic acid plus amoxycillin)
Monobactams	Aztreonam
Carboxypenems	Imipenem
Aminoglycosides	Streptomycin, Kanamycin, Neomycin, Gentamycin, Tobramycin, Amikacin and Netilmicin
	Gentamicin
Glycopeptides	Vancomycin
Lincomycins	Clindamycin
Macrolides and Azalides	Azithromycin, Clarithromycin, Clindamycin, Erythromycin, Lincomycin, Roxithromycin, Dirithromycin, Spiramycin and Josamycin
Polypeptides	Bacitracin, Colistin, Polymyxin B
	Bacitracin
Rifamycins	Rifampicin
Tetracyclines	Tetracycline, Chlortetracycline, Oxytetracycline, Demeclocycline and Minocycline
Semisynthetic Tetracyclines	Doxycycline
Chloramphenicol	Chloramphenicol
Fluoroquinolones and Quinolones	Ciprofloxacin (Cipro®), Enoxacin, Grepafloxacin, Levofloxacin, Lomefloxacin, Norfloxacin, Ofloxacin, Sparfloxacin, Trovafloxacin, Cinoxacin and Nalidixic acid
Lincosamides	clindamycin (Cleocin®)

Table 3: Classes and Examples of Antibiotic Otic Agents	
Antibiotic Class	Examples
Oxazolidinones	linezolid (Zyvox®)
Aminocyclitols	Spectinomycin (Trobicin®)
Cycloserines	
Mupirocin	
Streptogramins	Quinupristin and dalfopristin (Synercid®)
Urea hydroxamates	
Heteroaromatic polycycles	
Folic Acid Analogs	Trimethoprim and Trimethoprim-sulfamethoxazole (TMP-SMX)
Sulfa Drugs (sulfonamides)	Sulfanilamide, Sulfadiazine, sulfamethoxazole, Sulfisoxazole, Sulfamethizole, Silver sulfadiazine and Mafenide

[000197] Still other otic agents encompassed by the methods and compositions of present invention include antiviral medications. Antivirals are effective in combination with a Cox-2 inhibitor to reduce the virulence and proliferation of a viral infection-related otic disorder, in addition to reducing the resultant inflammation.

[000198] Also encompassed by the present invention are the antifungal otic agents. Antifungal agents kill or suppress the growth of a fungus in a fungal infection-related otic disorder. The combination therapy comprising an antifungal agent and a Cox-2 inhibitor reduces the symptoms of a fungal infection-related otic disorder by suppressing fungal growth and lowering inflammation.

[000199] Some otic agents, however, do not comprise antibiotics, antifungals, or antivirals. These agents rely on pH or another physical chemical property of the agent to control the spread of or prevent the occurrence of an infection-related otic disorder.

[000200] Further encompassed by the methods and compositions of the present invention include the astrigent class of otic agents used for treating or preventing otic disorders. As used herein, the term "astrigent" or "drying agent," used interchangeably herein, means any chemical or drug that cause shrinkage of the skin and mucous membranes. Astrigents act by precipitating the proteins on the surface layer of the skin and mucus membranes. Their main use is to stop seepage, weeping, or discharge from mucous membranes. For example, the astrigent, isopropyl alcohol, is effective to dry the membranes lining the ear canal, which reduces the chance of an infection-related otic disorder developing.

[000201] Still further encompassed by the methods and compositions of the present invention include the antiseptic class of otic agents. Antiseptics such as acetic acid drops, for example, are an affective antiseptic that kill or suppresses the growth of bacteria, which are susceptible to low pH environments.

[000202] Otic agents such as antihistamines and decongestants are also encompassed by the compositions and methods of the present invention as vasoconstrictors for the improvement of eustachian tube function. For example, such otic agents as phenylephrine 0:25% may be instilled into each nasal cavity 3 drops every 3 hours in combination with a Cox-2 inhibitor while the subject suffering from an otic disorder is supine with the neck extended. See, *The Merck Manual, Sec. 7. Chap 83-85,* 17th Edition. Likewise, decongestants, such as ephedrine sulfate, pseudoephedrine, or phenylpropanolamine may be administered at 30 mg by mouth every 4 to 6 hours in combination with a Cox-2 inhibitor. *Id.*

[000203] Moreover, if allergy is considered a significant factor underlying the otic disorder in a subject, antihistamines, such as, for example, chlorpheniramine 4 mg by mouth every 4 to 6 hours, may be administered to the subject in combination with a Cox-2 inhibitor to improve eustachian tube function.

[000204] Also encompassed by the present invention are anaesthetic otic agents. For example, topical anesthetics can optionally be mixed with

penetration enhancers to relieve the pain associated with otic disorders. Likewise, local anesthetics, usually injectable, are effective otic agents by producing a reversible block to conduction along the nerve fiber leading to the otic region. This block is effective in reducing the pain associated with an otic disorder. Anesthetics, both topical and injectable, that are used for treating the pain associated with having an otic disorder are considered otic agents for purposes of the present invention.

[000205] Other otic agents that also assist in reducing the pain a subject suffers from an otic disorder includes the corticosteroids. Corticosteroids not only help reduce pain, but also, help to reduce the inflammation associated with many otic disorders.

[000206] Although, any combination of a Cox-2 inhibitor and otic agent is encompassed by the present invention, preferred examples of otic agents include those agents specifically recited in tables 3 and 4. Thus, it is further preferred that any otic agent recited in tables 3 and 4 be combined in methods, compositions, pharmaceutical compositions, and kits with any inhibitor of the Cox-2 enzyme. More preferred still are combinations of Cox-2 inhibitors with one or more otic agents. Even further preferred are methods, compositions, pharmaceutical compositions, and kits comprising Cox-2 inhibitors alone and in combination with one or more otic agents.

Table 4

Table 4: Otic Agents						
No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A1	neomycin sulfate		antibiotic	0.5%		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*
A2	polymyxin B sulfate		antibiotic	10,000 U/mL		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*
A3	hydrocortisone		corticosteroid	1%		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*
A4	penicillin		Beta-lactam antibiotic	250 -500 mg		Mygind, N., *et al.* Clin. Otolaryngol.;6:5-13 (1981).
A5	aluminum acetate solution (Burow's solution)		antiseptic	0.35%		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*
A6	penicillin G					
A7	penicillin V					
A8	procaine					
A9	benzathine					
A10	cloxacillin					
A11	dicloxacillin					
A12	methicillin					
A13	phenylephrine		decongestant	0.25% to 1.0%		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*
A14	amoxicillin	Amoxil	antibiotic	35 to 80 mg/kg/day		Chaput de Saintonge, D., *et al.*, *Br Med J*;284:1078-81 (1982).
A15	sulfisoxazole		antibiotic	150 mg/kg		*The Merck Manual, Sec. 7. Chap 83-85,17th Edition.*

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A16	nafcillin					
A17	oxacillin					
A18	trimethoprim and sulfamethoxazole (TMP-SMX)	Bactrim	antibiotic	160/800 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A19	ceftriaxone			50 mg/kg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A20	cefaclor		Cephalosporin antibiotic	250 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A21	cefuroxime			500 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A22	clavulanate potassium			100 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A23	clarithromycin	Biaxin	macrolide antibiotic	250 – 500 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A24	cefixime		cephlasporin antibiotic	200 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A25	ephedrine sulfate		decongestant	30 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A26	pseudoephedrine		decongestant	30 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A27	phenylpropanolamine		decongestant	30 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A28	chlorpheniramine		antihistamine	4 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A29	loratadine		antihistamine	10 mg/day		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A30	scopolamine		anticholinergic drugs	400 – 800 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A31	atropine		anticholinergic drugs	20 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A32	glycopyrrolate			1 or 2 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A33	prochlorperazine			25 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A34	diphenhydramine		antihistamine	50 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A35	meclizine	Antivert		50 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A36	cyclizine			50 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A37	pentobarbital			100 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A38	diazepam	Valium		2 to 5 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A39	gentamicin		aminoglycoside antibacterial	> 1 mL 30 mg/mL		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A40	prednisone		corticosteroid	60 mg		*The Merck Manual, Sec. 7. Chap 83-85, 17th Edition.*
A41	ciprofloxacin/ hydrocortisone	Cipro HC	corticosteroid and antibiotic		Bayer Inc.	U.S. Patent No. 6,440,964 to Cagle, *et al.*
A42	ofloxacin	Ocuflox /Floxin Otic	antibiotic		Allergan	U.S. Patent No. 6,440,964 to Cagle, *et al.*

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A43	bis-(2-pyridyl-1-oxide) disulfide					U.S. Patent No. 4,370,325 to Packman
A44	botulinum toxin				Allergan Sales, Inc	United States Patent 6,358,926 Donovan
A45	moxifloxacin		Fluoroquinolone antibiotic		Alcon Laboratories, Inc.	United States Patent 6,395,746 Cagle, et al.
A46	trovafloxacin		quinolone antibiotic		Alcon Laboratories, Inc.	United States Patent 6,395,746 Cagle, et al.
A47	levofloxacin		fluoroquinolones		Alcon Laboratories, Inc.	United States Patent 6,395,746 Cagle, et al.
A48	Ticarcillin/ clavulanic acid	Timentin		3 grams/100 mg		
A49	mafenide		antibiotic			
A50	gatifloxacin		quinolone			U.S. Published Application No. 002022629 to Cagle, et al.
A51	grepafloxacin		quinolone			U.S. Published Application No. 002022629 to Cagle, et al.
A52	norfloxacin		oxazolidinones			U.S. Published Application No. 0020142999 to Cagle, et al.
A53	carbamide peroxide	Debrox	antiseptic	6.5%		
A54	chlorhexidine		antiseptic	2%		
A55	povidone iodine	betadine	antiseptic	10%		
A56	polyhyroxine iodine		antiseptic	0.5%		

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A57	acetic acid /hydrocortisone	Vosol HC	antiseptic and corticosteroid	2%/1%		
A58	benzocaine/antipyrine	Auralgan		1.4-5.0% Benzocaine and 5-5.4% antipyrine		
A59	benzocaine/antipyrine/ phenylephrine	Tympagesic				
A60	Burrows Solution w/acetic acid 2%	Domeboro	antiseptic			
A61	hydrocortisone 10 mg, neomycin sulfate 5 mg, polymyxin B sulfate 10,000 units/mL Otic Soln, Susp	Cortisporin Otic	corticosteroid and antibiotic			
A62	triethanolamine otic	Cerumenex				
A63	chloramphenicol	Chloromycet Otic Soln	antibiotic			
A64	colistin sulfate 3 mg, hydrocortisone acetate 10 mg, neomycin sulfate 5 mg/mL	Coly-Mycin S ® Otic	antibiotic and corticosteroid			
A65	acetic acid + propylene glycol	Vosol Otic	antiseptic and astrigent			
A66	benanomicin A		antifungal			Ohtsuka, K., *et al*, *J. Antimicrob. Chemother.*,39: 71-77 (1997).
A67	amphotericin B		antifungal			Ohtsuka, K., *et al*, *J. Antimicrob. Chemother.*,39: 71-77 (1997).
A68	fluconazole		antifungal			Ohtsuka, K., *et al*,

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
						J. Antimicrob. Chemother.,39: 71-77 (1997).
A69	tobramycin	Nebcin	antibiotic			Drug Evaluations, 6th Edition, (1986).
A70	ticarcillin	Ticar	antibiotic			Drug Evaluations, 6th Edition, (1986).
A71	phenylephrine		decongestant			Drug Evaluations, 6th Edition, (1986).
A72	phenylephrine/propylene glycol		decongestant and astrigent			Drug Evaluations, 6th Edition, (1986).
A73	benzocaine		anesthetic			Drug Evaluations, 6th Edition, (1986).
A74	aluminum acetate		antiseptic	2%		Drug Evaluations, 6th Edition, (1986).
A75	amphotericin B		antifungal			Drug Evaluations, 6th Edition, (1986).
A76	azlocillin					
A77	m-cresyl acetate		antiseptic			Drug Evaluations, 6th Edition, (1986).
A78	hydrocortisone, neomycin sulfate		antibiotic and corticosteroid			Drug Evaluations, 6th Edition, (1986).
A79	polymyxin B sulfate/ hydrocortisone		antibiotic and corticosteroid			Drug Evaluations, 6th Edition, (1986).
A80	rubbing alcohol isopropyl alcohol		astrigent	70%		Drug Evaluations, 6th Edition, (1986).
A81	lidocaine		anesthetics			Drug Evaluations, 6th Edition, (1986).
A82	tobramycin/ dexamethasone	Tobrex	antibiotic and corticosteroid			
A83	cresylate					
A84	sulfisoxazole		antibiotic			
A85	amoxicillin plus clavulanate potassium	Augmentin	antibiotic	125-875 mg/125 mg		

Table 4: Otic Agents						
No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A86	azithromycin	Zithromax	antibiotic			
A87	cefprozil	Cefzil	cephalosporin antibiotics	250 to 500 mg		
A88	cefpodoxime proxetil	Vantin	cephalosporin antibiotics			
A89	ceftibuten	Cedax	antibiotic			
A90	cefuroxime axetil	Ceftin	cephalosporin antibiotics	250 to 500 mg		Gooch, W., *et al., Pediatr. Infect. Dis. J.15*:157-64 (1996).
A91	clarithromycin	Biaxin	antibiotic			
A92	loracarbef	Lorabid	cephalosporin antibiotics	200 to 400 mg		
A93	carbenicillin					
A94	ceftriaxone sodium	Rocephin	cephalosporin antibiotic	50 mg/kg		Cohen, R., *et al., Pediatric Infectious Disease Journal* 18:403-409 (1999).
A95	ethanol		astrigent			
A96	colistin sulfate, neomycin sulfate, hydrocortisone acetate, thonzonium bromide	Cortisporin-TC Otic	antibiotic and corticosteroid and antiseptic			
A97	erythromycin plus sulfisoxazole		antibiotic			
A98	amoxicillin plus clavulanate		antibiotic			
A99	cefixime		antibiotic			
A100	cephradine		antibiotic			
A101	itraconazole	Sporanox	antifungal			
A102	clotrimazole	Lotrimin	antifungal			
A103	piperacillin					Drug Evaluations, 6th Edition, (1986).

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A104	boric acid		antiseptic			
A105	tolnaftate	Tinactin solution	antifungal			
A106		Mycolog cream	antifungal			
A107	ketoconazole		antifungal			
A108	cefdinir		antibiotic	7 mg/kg twice a day		Block, S., *et al., Pediatr. Infect. Dis. J. 19(12 Suppl)*:S153-8 (2000).
A109	levofloxacin	Levaquin®Tavanic®)	quinolone antibiotic			
A110	acetic acid, aluminum acetate, sodium acetate	Domeboro	astringent and antiseptic			
A111	colistin sulfate		antibiotic	3 mg		Drug Evaluations, 6th Edition, (1986).
A112	piperacillin + tazobactam		antibiotic			
A113	ticarcillin		antibiotic			
A114	mezlocillin		antibiotic			
A115	cefadroxil		antibiotic			
A116	cefazolin		antibiotic			
A117	cephalexin		antibiotic			
A118	cephalothin		antibiotic			
A119	cephapirin		antibiotic			
A120	cefamandole		antibiotic			
A121	cefmetazole		antibiotic			
A122	cefonicid		antibiotic			
A123	cefotetan		antibiotic			
A124	cefoxitin		antibiotic			
A125	cefepime		antibiotic			
A126	cefixime		antibiotic			
A127	cefoperazone		antibiotic			
A128	cefotaxime		antibiotic			

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A129	cefpodoxime		antibiotic			
A130	ceftazidime		antibiotic			
A131	ceftibuten		antibiotic			
A132	ceftizoxime		antibiotic			
A133	ceftriaxone		antibiotic			
A134	imipenem		antibiotic			
A135	meropenem		antibiotic			
A136	aztreonam		antibiotic			
A137	sulbactam		antibiotic			
A138	tazobactam		antibiotic			
A139	ampicillin + sulbactam		antibiotic			
A140	bacampicillin		antibiotic			
A141	clavulanic acid + amoxycillin		antibiotic			
A142	streptomycin		antibiotic			
A143	kanamycin		antibiotic			
A144	amikacin		antibiotic			
A145	netilmicin		antibiotic			
A146	vancomycin		antibiotic			
A147	clindamycin		antibiotic			
A148	lincomycin		antibiotic			
A149	roxithromycin		antibiotic			
A150	dirithromycin		antibiotic			
A151	spiramycin		antibiotic			
A152	josamycin		antibiotic			
A153	bacitracin		antibiotic			
A154	rifampicin		antibiotic			
A155	tetracycline		antibiotic			
A156	chlortetracyline		antibiotic			

Table 4: Otic Agents

No.	Generic Name	Trade Name(s)	Drug Class	Dose	Manufacturer	Reference
A157	oxytetracycline		antibiotic			
A158	demeclocycline		antibiotic			
A159	minocycline		antibiotic			
A160	doxycycline		antibiotic			
A161	enoxacin		antibiotic			
A162	lomefloxacin		antibiotic			
A163	sparfloxacin		antibiotic			
A164	linezolid		antibiotic			
A165	quinupristin + dalfopristin	Synercid	antibiotic			
A166	sulfanilamide		antibiotic			
A167	sulfadiazine		antibiotic			
A168	sulfamethizole		antibiotic			
A169	silver sulfadiazine		antibiotic			
A170		Neosporin®				
A171		Mycelex cream				
A172	flumethasone	corticosteroid				
A173	acetaminophen	Tylenol ®				

[000207] As described above, there are several otic agents that are available for an otic disorder treatment or prevention therapy comprising one or more otic agents and a Cox-2 inhibitor.

[000208] Examples of preferred classes of otic agents capable of treating or preventing the symptoms of an otic disorder in combination with a Cox-2 inhibitor include, but are not limited to, antibiotics, antifungals, astrigents, anticholinergics, corticosteroids, antiseptics, antivirals, decongestants, antihistamines and anaesthetics, and mixtures thereof.

[000209] For purposes of the present invention, otic agents such as antibiotics, for example, are combined with Cox-2 inhibitors as an effective co-therapy method for treating or preventing otic disorders. Likewise, otic agents such as antibiotics, for example, are combined with Cox-2 inhibitors in novel compositions for treating or preventing otic disorders.

[000210] Antibiotic medications improve the symptoms of a subject suffering from certain otic disorders by suppressing the growth of or killing the underlying infectious agent. In addition, antibiotic medications shorten the recovery time of a subject suffering from certain otic disorders.

[000211] It is preferred that the antibiotic class of otic agents comprises at least one compound selected from the group consisting of beta-lactam penicillins, beta-lactam cephalosporins, semisynthetic penicillins, clavulanic acid, monobactams, quinupristin plus dalfopristin, carboxypenems, aminoglycosides, glycopeptides, lincomycins, macrolides, polypeptides, polyenes, rifamycins, tetracyclines, chloramphenicol, fluoroquinolones, quinolones, lincosamides, oxazolidinones, aminocyclitols, cycloserines, mupirocin, streptogramins, urea hydroxamates, heteroaromatic polycycles, folic acid analogs, sulfonamides and azalides, and mixtures thereof.

[000212] More preferred is that the antibiotic comprises at least one compound selected from the group consisting of penicillin, penicillin G, penicillin V, procaine, benzathine, cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin, azlocillin, carbenicillin, piperacillin, piperacillin plus

tazobactam, ticarcillin, mezlocillin, cefadroxil, cefazolin, cephalexin, cephalothin, cephapirin, cephradine, cefaclor, cefamandole, cefmetazole, cefonicid, cefotetan, cefoxitin, cefprozil, cefuroxime, loracarbef, cefepime, cefixime, cefoperazone, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, Imipenem, meropenem, aztreonam, clavulanic acid, sulbactam, tazobactam, ampicillin, ampicillin plus sulbactam, amoxycillin, amoxicillin, amoxicillin plus clavulanate potassium, bacampicillin, clavulanic acid plus amoxycillin, aztreonam, imipenem, streptomycin, kanamycin, neomycin, gentamycin, tobramycin, amikacin, netilmicin, gentamicin, vancomycin, clindamycin, azithromycin, clarithromycin, clindamycin, roxithromycin, dirithromycin, spiramycin, josamycin, erythromycin, lincomycin, bacitracin, colistin, polymyxin B, bacitracin, amphotericin, nystatin, rifampicin, tetracycline, chlortetracycline, oxytetracycline, demeclocycline, minocycline, doxycycline, chloramphenicol, ciprofloxacin, enoxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin, cinoxacin, nalidixic acid, clindamycin, linezolid, spectinomycin, quinupristin, dalfopristin, trimethoprim, trimethoprim-sulfamethoxazole, sulfanilamide, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfamethizole, silver sulfadiazine and mafenide, and mixtures thereof.

[000213] It is preferred that the antifungal class of otic agents comprises at least one compound selected from the group consisting of imidazoles, triazoles, polyenes and allylamines, and mixtures thereof.

[000214] More preferred is that the antifungal comprises at least one compound selected from the group consisting of clotrimazole, griseofulvin, undecylenic, econazole, miconazole, ketaconazole, sulconazole, oxiconazole, fluconazole, itraconazole, nystatin, naftifine, terbinafine, ciclopirox, butenafine, haloprogin and tolnaftate, and mixtures thereof.

[000215] It is preferred that the antiviral class of otic agents comprises at least one compound selected from the group consisting of acyclovir, gancyclovir, interferons, mono and polyclonal antibodies, thimerasol, idoxuridine, vidarabine, trifluridine, famciclovir, valacyclovir, penciclovir,

ganciclovir, dipyridamole, impulsin, pleconaril, foscarnet, ribavirin, amantadine, rimantadine, cidofovir, ICI 130,685, zanamivir, oseltamivir, valganciclovir, aciclovir, idoxuridine, vidarabine and valacyclovir, and mixtures thereof.

[000216] It is preferred that the antihistamine class of otic agents comprises at least one compound selected from the group consisting of alkylamines, ethanolamines, piperazines, piperadines, ethylenediamines, phenothiazines and tricyclic antidepressants, and mixtures thereof.

[000217] More preferred is that the antihistamine comprises at least one compound selected from the group consisting of azatadine, meclizine, promethazine bromodiphenhydramine, brompheniramine, brompheniramine maleate, carbinoxamine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, phenindamine, pheniramine, phenyltoloxamine, pyrilamine, triprolidine, clemastine, dimenhydrinate, cetirizine, terfenadine, astemizole, loratadine, acrivastine, hydroxyzine, meclizine, compazine, imipramine, doxopin, amitryptoline, tripelennamine, fexofenadine and azatadine, and mixtures thereof.

[000218] It is preferred that the decongestant class of otic agents comprises at least one compound selected from the group consisting of ephedrine, ephinephrine, levodesoxyephedrine, oxymetazoline, naphazoline, phenylephrine, phenylpropanolamine, propylhexedrine, pseudoephedrine and xylometazoline, and mixtures thereof.

[000219] Also preferred is that the astrigent class of otic agents comprises at least one compound selected from the group consisting of isopropyl alcohol, ethanol and propylene glycol.

[000220] Further preferred is that the antiseptic class of otic agents comprises at least one compound selected from the group consisting of acetic acid, boric acid, gentian violet, hydrogen peroxide, carbamide peroxide, chlorhexidine, saline, mercurochrome, povidone iodine, polyhyroxine iodine, cresylate and aluminum acetate, and mixtures thereof.

[000221] Still further preferred is that the corticosteroid otic agent comprises at least one compound selected from the group consisting of hydrocortisone, prednisone, fluprednisolone, dexamethasone, betamethasone, betamethasone valerate, methylprednisolone, fluocinolone acetonide, flurandrenolone acetonide, fluorometholone, cortisone, prednisolone, alclometasone, amcinonide, betamethasone, clobetasol, clocortolone, desonide, desoximetasone, diflorasone, fluocinonide, flurandrenolide, fluticasone, halcinonide, halobetasol, mometasone, flumethasone, prednicarbate and triamcinolone, and mixtures thereof.

[000222] Also preferred is that the anaesthetic class of otic agents comprises at least one compound selected from the group consisting of benzocaine, butamben picrate, tetracaine, dibucaine, carbocaine, cocaine, chloroprocaine, mepivacaine, etidocaine, prilocaine, etidocaine, bupivicaine, lidocaine, fenamates, pyrrolealkanoic acids, pyrazolone derivatives, oxicams and pramoxine, and mixtures thereof.

[000223] Further preferred is that the anticholinergic class of otic agents comprises at least one compound selected from the group consisting of homatropine, scopolamine and atropine, and mixtures thereof.

[000224] In other preferred embodiments, any combination of the Cox-2 inhibitors and otic agents that are described above can be used in the novel methods, compositions, pharmaceutical compositions and kits of the present invention.

[000225] Therefore, in one embodiment, one or more of an antibiotic class of otic agent is combined with at least one Cox-2 inhibitor. In another embodiment, one or more of a corticosteroid is combined with at least one Cox-2 inhibitor. In still another embodiment, one or antiseptic otic agents are combined with at least one Cox-2 inhibitor. In yet another embodiment, one or more antifungal otic agents are combined with at least one Cox-2 inhibitor. In another embodiment, one or more antiviral otic agents are combined with at least one Cox-2 inhibitor. In still another

embodiment, one or more anticholinergic otic agents are combined with at least one Cox-2 inhibitor. In another embodiment, one or more astrigent otic agents are combined with at least one Cox-2 inhibitor. In another embodiment, one or more decongestant otic agents are combined with at least one Cox-2 inhibitor. In yet another embodiment, one or more antihistamine otic agents are combined with at least one Cox-2 inhibitor. In yet another embodiment, one or more anaesthetic otic agents are combined with at least one Cox-2 inhibitor.

[000226] Further encompassed by the present invention are any combinations of one or more of antibiotic, antifungal, astrigent, anticholinergic, antiseptic, antiviral, decongestant, antihistamine and anaesthetic agents, each independently, or any combinations thereof, that are also combined with at least one Cox-2 inhibitor.

[000227] In another preferred embodiment, a Cox-2 inhibitor such as, for example, celecoxib, can be combined with any of the aforementioned otic agents cited in table 3 and table 4, including, for example, the beta-lactam semisynthetic penicillin, amoxicillin.

[000228] In one embodiment, the present invention encompasses a novel therapuetic composition comprising a Cox-2 inhibitor and an otic agent.

[000229] In another embodiment, the present invention encompasses a pharmaceutical composition for preventing and treating an otic disorder or an otic disorder-related complication in a subject that is in need of such prevention or treatment, the pharmaceutical composition comprising a Cox-2 inhibitor, an otic agent, and a pharmaceutically acceptable carrier.

[000230] In the present invention, a composition comprising a Cox-2 inhibitor alone or in combination with an otic agent is administered to a subject in need of such prevention or treatment according to standard routes of drug delivery that are well known to one of ordinary skill in the art.

[000231] Each of the Cox-2 inhibitors and otic agents of the present invention can be supplied in the form of a salt, or prodrug, if desirable.

Cox-2 inhibitors and otic agents that are useful in the present invention can be of any purity or grade, as long as the preparation is of a quality suitable for pharmaceutical use. The Cox-2 inhibitors and otic agents can be provided in pure form, or it can be accompanied with impurities or commonly associated compounds that do not affect its physiological activity or safety.

[000232] The Cox-2 inhibitors and otic agents can be supplied as pure compounds, or in the form of a pharmaceutically active salt. The Cox-2 inhibitors and otic agents can also be supplied in the form of a prodrug, an isomer, a racemic mixture, or in any other chemical form or combination that, under physiological conditions, still provides for inhibition of the Cox-2 enzyme.

[000233] The combination of a Cox-2 inhibitor and a otic agent can be provided in a pharmaceutically acceptable carrier or excipient to form a pharmaceutical composition. Pharmaceutically acceptable carriers and excipients include, but are not limited to, physiological saline, Ringer's solution, phosphate solution or buffer, buffered saline and other carriers known in the art. Pharmaceutical compositions may also include stabilizers, anti-oxidants, colorants, and diluents. Pharmaceutically acceptable carriers and additives are chosen such that side effects from the pharmaceutical compound are minimized and the performance of the compound is not canceled or inhibited to such an extent that treatment is ineffective. In one embodiment, the Cox-2 inhibitor and the otic agent are administered to a subject together in one pharmaceutical carrier. In another embodiment, they are administered separately.

[000234] The pharmaceutical compositions may be administered enterally and parenterally. Oral (intra-gastric) is a preferred route of administration. Pharmaceutically acceptable carriers can be in solid dosage forms for the methods of the present invention, which include tablets, capsules, pills, and granules, which can be prepared with coatings and shells, such as enteric coatings and others well known in the art.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs.

[000235] Parenteral administration includes subcutaneous, intramuscular, intradermal, intramammary, intravenous, and other administrative methods known in the art. Enteral administration includes solution, tablets, sustained release capsules, enteric-coated capsules, and syrups. When administered, the pharmaceutical composition may be at or near body temperature.

[000236] Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate, granulating and disintegrating agents, for example, maize starch, or alginic acid, binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid, or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

[000237] Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients are mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients are present as such, or mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

[000238] Aqueous suspensions can be produced that contain the active materials in a mixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone gum tragacanth and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

[000239] The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, or one or more sweetening agents, such as sucrose or saccharin.

[000240] Oily suspensions may be formulated by suspending the active ingredients in an omega-3 fatty acid, a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol.

[000241] Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[000242] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already

mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[000243] Syrups and elixirs containing the Cox-2 inhibitor and/or otic agent may be formulated with sweetening agents, for example glycerol, sorbitol, or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

[000244] The subject method of prescribing a Cox-2 inhibitor and/or otic agent and compositions comprising the same can also be administered parenterally, either subcutaneously, or intravenously, or intramuscularly, or intrasternally, or by infusion techniques, in the form of sterile injectable aqueous or olagenous suspensions. Such suspensions may be formulated according to the known art using those suitable dispersing of wetting agents and suspending agents which have been mentioned above, or other acceptable agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, n-3 polyunsaturated fatty acids may find use in the preparation of injectables.

[000245] Administration can also be by inhalation, in the form of aerosols or solutions for nebulizers, or rectally, in the form of suppositories prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature, but liquid at the rectal temperature and will therefore, melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

[000246] Also encompassed by the present invention is buccal or "sub-lingual" administration, which includes lozenges or a chewable gum comprising the compounds, set forth herein. The compounds can be

deposited in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the compounds in an inert base such as gelatin and glycerin or sucrose and acacia.

[000247] Other methods for administration of the Cox-2 inhibitor compound and the otic agent include dermal patches that release the medicaments directly into a subject's skin.

[000248] Topical delivery systems are also encompassed by the present invention and include ointments, powders, sprays, creams, jellies, collyriums, solutions or suspensions.

[000249] Powders have the advantage of sticking to moist surfaces, and consequently, can remain in the otic canal for long periods. Therefore, powders are especially attractive for chronic suppurative otitis media.

[000250] Creams are used, primarily, in the treatment of otic disorders of the external auditory canal. Aminoglycoside antibiotic ointments, such as neosporin and/or tobramycin, can be utilized as combination therapies with Cox-2 inhibitors for external otitis. Mycelex cream is an example of a frequently chosen otic agent cream preparation for the treatment of candida infections of the external auditory canal that can be utilized in combination with a Cox-2 inhibitor.

[000251] The most commonly used otic preparations are drops. Drops are mainly utilized in two forms, as a Cox-2 inhibitor agent or as combinations of otic agents and Cox-2 inhibitors.

[000252] The compositions of the present invention can optionally be supplemented with additional agents such as, for example, viscosity enhancers, preservatives, surfactants and penetration enhancers.

[000253] Viscosity is an important attribute of ototopical medications. Drops that have a high viscosity tend to stay in the auditory canal for longer periods and thus, increase absorption of the active compounds by the target tissues or increase the retention time ear. Such viscosity-building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methylcellulose, hydroxy propyl methylcellulose, hydroxyethyl

cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents know to those skilled in the art. Such agents are typically employed at a level of from 0.01% to 2% by weight.

[000254] Preservatives are optionally employed to prevent microbial contamination during use. Suitable preservatives include: polyquaternium-1, benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, or other agents known to those skilled in the art. The use of polyquaternium-1 as the antimicrobial preservative is preferred. Typically, such preservatives are employed at a level of from 0.001% to 1.0% by weight.

[000255] The solubility of the components of the present compositions may be enhanced by a surfactant or other appropriate co-solvent in the composition. Such co-solvents include polysorbate 20, 60, and 80, polyoxyethylene/polyoxypropylene surfactants (*e.g.* Pluronic F-68, F-84 and P-103), cyclodextrin, or other agents known to those skilled in the art. Typically, such co-solvents are employed at a level of from 0.01% to 2% by weight.

[000256] A penetration enhancer is an agent used to increase the permeability of the skin to an active agent to increase the rate at which the drug diffuses through the skin and enters the tissues and bloodstream. Thus, in one embodiment of the present invention, a penetration enhancer may be added to a Cox-2 inhibitor topical composition or a Cox-2 inhibitor and otic agent topical composition.

[000257] Examples of penetration enhancers suitable for use with the compositions of the present invention include: alcohols, such as ethanol and isopropanol; polyols, such as n-alkanols, limonene, terpenes, dioxolane, propylene glycol, ethylene glycol, other glycols, and glycerol; sulfoxides, such as dimethylsulfoxide (DMSO), dimethylformamide, methyl dodecyl sulfoxide, dimethylacetamide; esters, such as isopropyl myristate/palmitate, ethyl acetate, butyl acetate, methyl proprionate, and capric/caprylic triglycerides; ketones; amides, such as acetamides; oleates, such as triolein; various surfactants, such as sodium lauryl sulfate;

various alkanoic acids, such as caprylic acid; lactam compounds, such as azone; alkanols, such as oleyl alcohol; dialkylamino acetates, and admixtures thereof.

[000258] Pharmaceutically acceptable excipients and carriers encompass all the foregoing and the like. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. *See e.g.* Gennaro, A. R., Remington: The Science and Practice of Pharmacy, 20th Edition, (Lippincott, Williams and Wilkins), 2000; Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania, 1975; Liberman, *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, *et al.*, Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

[000259] For purposes of the present invention, it is preferred that the amount of a Cox-2 inhibitor that is administered to a subject comprises an effective amount of a Cox-2 inhibitor. It is further preferred that the amount of a Cox-2 inhibitor and the amount of an otic agent together comprise an effective amount of the combination of the two treatment agents. Still further preferred is that the amount of the monotherapy with the Cox-2 inhibitor comprise a therapeutically amount of the Cox-2 inhibitor. Further preferred is that the amount of the co-therapy with the Cox-2 inhibitor and otic agent comprises a therapeutically effective amount of the co-therapy.

[000260] Thus, the present invention encompasses a method of preventing and treating an otic disorder and an otic disorder-related complication in a subject in need of such prevention and treatment, the method comprising administering an amount of a Cox-2 inhibitor and an amount of an otic agent wherein the amount of the Cox-2 inhibitor and the amount of the otic agent together comprises a therapeutically effective amount.

[000261] As used herein, an "effective amount" means the dose or amount to be administered to a subject and the frequency of administration to the subject, which is readily determined by one having ordinary skill in the art, by the use of known techniques and by observing results obtained under analogous circumstances.

[000262] In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to, the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances.

[000263] As used herein, the terms "therapeutically effective" are intended to qualify the amount of an agent for use in therapy that will achieve the goal of preventing, or improvement in the severity of, the disorder being treated, while avoiding adverse side effects typically associated with alternative therapies. An otic disorders symptom or an otic disorder-related complication symptom is considered ameliorated or improved if any benefit is achieved, no matter how slight.

[000264] For example, any reduction in fever or pain of a subject suffering from an otic disorder such as otitis media would be considered an ameliorated symptom. Likewise, any inhibition or suppression of the normal infection and growth process for a bacterial or viral otic disorder would also be considered amelioration of an otic disorder. Furthermore, any reduction in symptom severity of an otic disorder-related complication is considered an ameliorated symptom.

[000265] As used herein, the terms "prophylactically effective" refer to an amount of a Cox-2 inhibitor alone or in combination with an otic agent that causes a decrease in the frequency of incidence of otic disorders or an otic disorder-related complication. The term "prophylactic" refers to the prevention of otic disorders or an otic disorder-related complication, whereas the term "therapeutic" refers to the effective treatment of an

existing disorder such as otic disorders or an otic disorder-related complication.

[000266] It will be appreciated that the amount of the Cox-2 inhibitor and the otic agent required for use in the treatment or prevention of otic disorders and otic disorder-related complications will vary within wide limits and will be adjusted to the individual requirements in each particular case. In general, for administration to adults, an appropriate daily dosage is described herein, although the limits that are identified as being preferred may be exceeded if expedient. The daily dosage can be administered as a single dosage or in divided dosages.

[000267] The appropriate dosage level of a Cox-2 inhibitor will generally be from about 0.01 mg per kg to about 140 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 mg/kg to about 25 mg/kg per day; more preferably about 0.5 mg/kg to about 10 mg/kg per day.

[000268] In larger mammals, for example humans, a typical indicated dose is about 0.5 mg to 7 grams orally per day. A compound may be administered on a regimen of several times per day, for example 1 to 4 times per day, preferably once or twice per day.

[000269] The amount of the Cox-2 inhibitor that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 7 g of active agent compounded optionally with an appropriate and convenient amount of carrier material, which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms for the Cox-2 inhibitor will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

[000270] The dosage level of an otic agent will necessarily depend on the particular agent that is used. However, in general, the appropriate

dosage level of an otic agent will generally be from about 0.0001 mg per kg to about 200 mg per kg subject body weight per day, which may be administered in single or multiple doses. Preferably, the dosage level will be about 0.001 mg per kg to about 100 mg per kg per day; more preferably about 0.01 mg per kg to about 50 mg per kg per day; even more preferably about 0.1 mg per kg to about 10 mg per kg subject body weight.

[000271] A combination therapy comprising an otic agent that is intended for the oral administration of humans may contain from about 10 micrograms to about 10 grams of active agent optionally compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. More preferably, the otic agent is dosed at between about 0.1 mg and about 1 gram. Even more preferably, the otic agent is dosed at between about 1 mg and about 750 mg. Even more preferably still, the otic agent is dosed at between about 100 mg and about 500 mg.

[000272] The exact dosage and regimen for administering a Cox-2 inhibitor alone or in combination with an otic agent will necessarily depend upon the potency and duration of action of the compounds used, the nature and severity of the illness to be treated, as well as the sex, age, weight, general health and individual responsiveness of the patient to be treated, and other relevant circumstances. Those skilled in the art will appreciate that dosages may also be determined with guidance from Goodman & Goldman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), Appendix II, pp. 1707-1711.

[000273] To determine the effectiveness of a particular dosage of a Cox-2 inhibitor alone and in combination with an otic agent is to monitor the effect of a given dosage on the progress or prevention of a particular otic disorder.

[000274] For example, one method to detect whether a subject is suffering from an otic disorder, such as an ear infection, is to look in the ear with an otoscope. An otoscope is a lighted instrument that allows the

physician to examine the outer ear and the eardrum. Redness or swelling of the eardrum is typical of an inflammatory response due to an infection.

[000275] Another method to diagnose and monitor an otic disorder is to check for the presence of middle ear fluid. The use of a special type of otoscope, called a pneumatic otoscope, allows the physician to blow a puff of air onto the eardrum to test eardrum movement. An eardrum with fluid build-up behind it does not move as well as an eardrum with air behind it.

[000276] Yet another method is to employ a test of middle ear function called tympanometry. This test requires insertion of a small soft plug into the opening of the subject's ear canal. The plug contains a speaker, microphone and a device that is able to change the air pressure in the ear canal, allowing for several measures of middle ear function. The subject feels air pressure changes in the ear or hears a few brief tones. While this test provides information on the condition of the middle ear, it does not determine how well the subject hears. An audiologist, a person who is specially trained to measure hearing, can also perform a hearing test. Both tests are indicative of the progress of treating an otic disorder.

[000277] As used herein, the term "subject" for purposes of treatment includes any subject, and preferably is a subject who is in need of the treatment of otic disorders, or who needs treatment of an otic disorder-related complication. For purposes of prevention, the subject is any subject, and preferably is a subject that is at risk for, or is predisposed to, developing an otic disorder or an otic disorder-related complication. The subject is typically an animal, and yet more typically is a mammal. "Mammal", as that term is used herein, refers to any animal classified as a mammal, including humans, domestic and farm animals, zoo, sports, or pet animals, such as dogs, horses, cats, cattle, etc. Preferably, the mammal is a human.

[000278] As used herein, the terms "predisposed to an otic disorder or an otic disorder-related complication" and "at risk for an otic disorder or an otic disorder-related complication," both of which are used interchangeably herein, mean any subject at risk for developing otic disorders or any otic

disorder-related complication. The subject may be a human subject who is at risk for developing otic disorders or an otic disorder-related complication. The subject may be at risk due to genetic predisposition, diet, age, exposure to a head truama, exposure to a potentially traumatic environment, exposure to otic disorder-causing agents, and the like. The subject may also be at risk due to physiological factors such as anatomical and biochemical abnormalities in the ear. For example, children are considered at risk for developing otic disorders due to certain anatomical differences found within their ears as compared to adults.

[000279] As used herein, the terms "subject is in need of the prevention or treatment of an otic disorder or otic-disorder-related complication" refer to any subject who is suffering from or is predisposed to otic disorders or any otic disorder-related complication described herein. The terms "subject is in need of the prevention or treatment of an otic disorder or otic-disorder-related complication" also refer to any subject that requires a lower dose of otic agents. In addition, the terms "subject is in need of the prevention or treatment of an otic disorder or otic-disorder-related complication" mean any subject who requires a reduction in the side-effects of an otic agent. Furthermore, the terms "subject is in need of the prevention or treatment of an otic disorder or otic-disorder-related complication" mean any subject who requires improved tolerability to any otic agent for otic disorders therapy.

[000280] In other preferred embodiments, the present invention encompasses a kit for preventing or treating otic disorders or an otic disorder-related complication in a subject that is in need of such prevention or treatment, the kit comprising one dosage form comprising a Cox-2 inhibitor and a second dosage form comprising an otic agent.

[000281] A therapy comprising a Cox-2 inhibitor alone and in combination with an otic agent encompasses the treatment and prevention of such otic disorder symptoms as, for example, otic pain, inflammation, otorrhea, otalgia, fever, and otic bleeding in a subject suffering from such symptoms.

[000282] As used herein, the terms "otic disorder" is defined as having any disorder or disease of the ear or even a post-surgical condition of the ear. Otic disorders include any condition of the ear that does not normally occur in or on the ear. As used herein, the term "ear" includes any component or structure found within or on the inner, middle and outer ear.

[000283] The terms "otic disorder" also include any complications that arise from having such a disorder. For example, meningitis may develop from a prolonged untreated otic infection disorder. Thus, the terms "otic disorder," "otic disorder complication" and "otic disorder-related complication," used interchangeably herein, includes any subsequent disease, disorder, injury or condition that may arise from having an otic disorder. The term "otic disorder-related complication" refers to any condition where developing an otic disorder is a risk factor for developing health complications.

[000284] For example, excess inflammation and swelling in a subject's ear may arise from an otic disorder. If the otic disorder is left untreated, the swelling and inflammation can, over time, depress certain nerves leading to an otic disorder-related complication, such as a temporary loss of hearing. However, the compositions and methods of the present invention may prevent and treat such a complication by reducing the swelling and the inflammation or by suppressing the growth of any underyling infectious agents. A Cox-2 inhibitor alone or in combination with a corticosteroid or an antibacterial agent would be an example of a novel composition and method suitable for treating the otic disorder-related complication of temporary hearing loss.

[000285] Otic disorders may arise in a subject via several determinants including environmental conditions, trauma, infectious agents, and genetics. The methods and compositions of the present invention are intended to treat a subject suffering from an otic disorder regardless of how the disorder first arose. Nevertheless, the majority of otic disorders arise via infectious agents.

[000286] An example of an otic disorder triggered by an infectious agent is otitis media. A bacterial otic infection can arise as a primary infection or it can also arise secondary to a viral infection. Thus, an otic agent, such as an antibiotic treatment, would be expected to have efficacy against many of the causative organisms of otitis media.

[000287] However, inflammation in the middle ear mucosa, typically caused by bacterial pathogens, is the primary event in the middle ear predisposing the development of the otic disorder, otitis media with effusion. Accordingly, the methods and compositions of the present invention encompass the treatment and prevention of not only the underlying otic disorder, but also the corresponding pain and inflammation in a subject who may already have or who may be predisposed to developing an otic disorder.

[000288] In a preferred embodiment, otic disorders that may be treated with the compositions and methods described herein, include one or more of, but are not limited to otic pain, inflammation, otorrhea, otalgia, fever, otic bleeding, Lermoyez's syndrome, Meniere's disease, vestibular neuronitis, benign paroxysmal positional vertigo, herpes zoster oticus, Ramsay Hunt's syndrome, viral neuronitis, ganglionitis, geniculate herpes, labyrinthitis, purulent labyrinthitis, viral endolymphatic labyrinthitis, perilymph fistulas, noise-induced hearing loss, presbycusis, drug-induced ototoxicity, acoustic neuromas, aerotitis media, infectious myringitis, bullous myringitis, otitis media, otitis media with effusion, acute otitis media, secretory otitis media, serous otitis media, acute mastoiditis, otitis extema, otosclerosis, squamous cell carcinoma, basal cell carcinoma, nonchromaffin paragangliomas, chemodectomas, globus jugulare tumors, globus tympanicum tumors, external otitis, perichondritis, aural eczematoid dermatitis, malignant external otitis, subperichondrial hematoma, ceruminomas, impacted cerumen, sebaceous cysts, osteomas, keloids, otalgia, tinnitus, vertigo, tympanic membrane infection, typanitis, otic furuncles, otorrhea, acute mastoiditis, petrositis, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis,

subdural empyema, otitic hydrocephalus, Dandy's syndrome, bullous myringitis, cerumen-impacted, diffuse external otitis, foreign bodies, keratosis obturans, otic neoplasm, otomycosis, trauma, acute barotitis media, acute eustachian tube obstruction, post-otic surgery, postsurgical otalgia, cholesteatoma, conductive and sensorineural hearing loss, epidural abscess, lateral sinus thrombosis, subdural empyema and otitic hydrocephalus.

[000289] More preferably, the methods and compositions of the present invention encompass the prevention and treatment of the otic disorders selected from the group consisting of otitis media, typanitis, myringitis, otitis media with effusion, external otitis and labyrinthitis.

[000290] Even more prefered yet, the methods and compositions of the present invention encompass the prevention and treatment of the otic disorder, otitis media.

[000291] The present invention also encompasses the therapeutic treatment and prevention of several otic disorder-related complications. Having an otic disorder, especially a chronic otic disorder, predisposes a subject to certain health risks that increase as the severity of a subject's otic disorder increases.

[000292] Increased health complications incident to having an otic disorder include otic disorder-related complications such as, but are not limited to, temporary and permanent hearing loss, mastoiditis, ruptured eardrums, brain abscesses, meningitis, chronic otitis media, facial paralysis, cholesteatomas, and calcification of the middle and inner ear, and including any other disorders or complications that are amenable to amelioration through inhibition of the Cox-2 enzyme alone or in combination with administration to a subject in need of such treatment of an effective amount of an otic agent referred to herein.

[000293] Preferably, the methods and compositions of the present invention encompass the prevention and treatment of such otic disorder-related complications as meningitis and facial paralysis.

[000294] The methods and compositions of the present invention not only encompass the prevention or treatment of otic disorders and otic disorder-related disorders in humans, but also in several animals. For example, many animals also suffer adverse consequences related to otic disorders. Moreover, ear infections in dogs respond to the same treatment used in humans. Accordingly, besides being useful for humans, the methods and compositions of the present invention also encompass the treatment and prevention of otic disorders and otic disorder-related disorders in other mammals, including horses, dogs, cats, rats, mice, sheep, pigs, cattle, hamsters, gerbils, and the like.

[000295] The following examples describe embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples, all percentages are given on a weight basis unless otherwise indicated.

EXAMPLE 1

[000296] This example shows the preparation of celecoxib.

[000297] Step 1: Preparation of 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione.

[000298] Following the disclosure provided in U.S. Patent No. 5,760,068, 4'-Methylacetophenone (5.26 g, 39.2 mmol) was dissolved in 25 mL of methanol under argon and 12 mL (52.5 mmol) sodium methoxide in methanol (25%) was added. The mixture was stirred for 5 minutes and 5.5 mL (46.2 mmol) ethyl trifluoroacetate was added. After refluxing for 24 hours, the mixture was cooled to room temperature and concentrated. 100 mL 10% HCl was added and the mixture extracted with 4 x 75 mL ethyl acetate. The extracts were dried over $MgSO_4$, filtered and concentrated to afford 8.47 g (94%) of a brown oil which was carried on without further purification.

[000299] Step 2: Preparation of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

[000300] To the dione from Step 1 (4.14 g, 18.0 mmol) in 75 mL absolute ethanol, 4.26 g (19.0 mmol) 4-sulphonamidophenylhydrazine hydrochloride was added. The reaction was refluxed under argon for 24 hours. After cooling to room temperature and filtering, the reaction mixture was concentrated to afford 6.13 g of an orange solid. The solid was recrystallized from methylene chloride/hexane to give 3.11 g (8.2 mmol, 46%) of the product as a pale yellow solid, having a melting point (mp) of 157°-159°C; and a calculated composition of C_{17} H_{14} N_3 O_2 SF_3 ; C, 53.54; H, 3.70; N, 11.02. The composition that was found by analysis was: C, 53.17; H, 3.81; N, 10.90.

EXAMPLE 2

[000301] This illustrates the production of a composition containing celecoxib and an antibiotic, and of a pharmaceutical composition containing the combination.

[000302] An antibiotic such as Penicillin V, may be supplied by any one of several commercially available preparations. One such preparation is Beepen VK 500mg®.

[000303] Beepen VK 500mg® is available from the GlaxoSmith Kline, Research Triangle Park, N.C. Each tablet of Beepen VK ® contains 500mg of penicillin V potassium.

[000304] Celecoxib can be prepared as described in Example 1, or it can be obtained under the trade name Celebrex® from Pharmacia Corporation, Peapack, NJ.

[000305] A therapeutic composition of the present invention can be formed by intermixing penicillin V potassium, 500 g; and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a suspension or solution with a sterile pharmaceutically acceptable liquid.

[000306] After mixing, the combination of penicillin V potassium and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 500 mg of penicillin V potassium and about 200 mg of celecoxib.

[000307] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains can contain about the same amount of the active ingredients as each of the single dose units of the liquid preparation described above.

[000308] Therapeutic and pharmaceutical compositions comprising a combination of any of the Cox-2 selective inhibitors and any of the sources of otic agent active ingredients that are described above can be formed by similar methods.

EXAMPLE 3

[000309] This illustrates the production of a composition containing celecoxib and the combination of an antihistamine and a decongestant and of a pharmaceutical composition containing the combination.

[000310] The combination of an antihistamine and a decongestant may be supplied by any one of several commercially available preparations. One such preparation is Claritin-D 12 hour® and Claritin-D 24 hour®.

[000311] Claritin-D 12 hour® is available from the Schering-Plough Corporation, Kenilworth, NJ. Each tablet of Claritin-D 12 hour® contains 5 mg loratadine and 120 mg pseudoephedrine sulfate.

[000312] Celecoxib can be prepared as described in Example 1, or it can be obtained under the trade name Celebrex® from Pharmacia Corporation, Peapack, NJ.

[000313] A therapeutic composition of the present invention can be formed by intermixing loratadine, 5 g; pseudoephedrine sulfate, 120 g; and

4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a suspension or solution with a sterile pharmaceutically acceptable liquid.

[000314] After mixing, the combination of loratadine, pseudoephedrine sulfate and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 5 mg of loratadine, 120 mg pseudoephedrine sulfate and about 200 mg of celecoxib.

[000315] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains can contain about the same amount of the active ingredients as each of the single dose units of the liquid preparation described above.

[000316] Therapeutic and pharmaceutical compositions comprising a combination of any of the Cox-2 selective inhibitors and any of the sources of otic agent active ingredients that are described above can be formed by similar methods.

EXAMPLE 4

[000317] This illustrates the production of a composition containing celecoxib and aciclovir, and of a pharmaceutical composition containing the combination.

[000318] Aciclovir (acyclovir) is available in the form of capsules, tablets and as a suspension under the trade name Zovirax® from GlaxoSmithKline, Research Triangle Park, NC. Celecoxib can be prepared as described in Example 1, or it can be obtained under the trade name Celebrex® from Pharmacia Corporation, Peapack, NJ.

[000319] A therapeutic composition of the present invention can be formed by intermixing solid or powdered aciclovir (400 g, available as

Zovirax®, from GlaxoSmithKline), and 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide (200 g, as produced in Comparative Example 1, or as available from Pharmacia Corporation, Peapack, NJ, under the tradename Celebrex®), in a laboratory mill or mixing device suitable for intimate mixing of powders without substantial generation of shear or temperature sufficient to degrade either of the two compounds. After mixing, the combination of aciclovir and celecoxib forms a therapeutic composition that is sufficient for the production of about 1000 human single dose units. Each single dose unit contains about 400 mg of aciclovir and about 200 mg of celecoxib.

[000320] If desirable, a solid carrier and other materials may be intermixed with the therapeutic composition to form a pharmaceutical composition and the resulting pharmaceutical composition may be formed into capsules for human consumption, for example, by conventional capsule-forming equipment, where each capsule contains 400 mg of aciclovir and 200 mg celecoxib.

[000321] Alternatively, the aciclovir (preferably in the form of a suspension) and the celecoxib may be dissolved or suspended into a liquid carrier, such as, for example, normal saline solution, to form a pharmaceutical composition suitable for human consumption. A single dosage of the liquid pharmaceutical composition for human use would be a volume sufficient to provide 400 mg of aciclovir and 200 mg of celecoxib.

[000322] Therapeutic and pharmaceutical compositions comprising a combination of any of the Cox-2 selective inhibitors and any of the otic agent active ingredients that are described above can be formed by similar methods.

[000323] All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by

their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

[000324] In view of the above, it will be seen that the several advantages of the invention are achieved and other advantageous results obtained.

[000325] As various changes could be made in the above methods and compositions without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.